SURGERY

VOL. 10 DECEMBER, 1941 NO. 6

Original Communications

THE MECHANISMS OF GASTRIC SECRETION*

A. C. IVY, PH.D., M.D.,† CHICAGO, ILL.

THE problem of the mechanisms of gastric secretion is of obvious academic interest. From the clinical viewpoint it is of interest because when we know the mechanisms of a biologic process, we usually are able to understand and to control variations from the normal, or to make an etiological diagnosis and to apply etiological therapy. Or, to express the idea more simply, situations arise clinically in which we should like to turn gastric secretion on or off at will. At the present time we have to be satisfied with neutralizing and buffering the secretion, or resecting the acid-secreting portion of the stomach, or replacing the water and acid chloride lost externally by water and salt given by clysis. At least we should find some harmless way to turn off a hypercontinuous secretion. Dr. Judd stated the problem just that way to me some twelve years ago when I was telling him of some of the academic questions pertaining to gastric secretion which I was studying. Since that time we have made some progress.

The subject of the mechanisms of gastric secretion is at present complicated because certain important questions cannot be answered. When these questions are answered, the subject will be relatively simple and can be outlined on one or two typewritten pages. *Because the subject is now complicated, I suspect that portions of it cannot be understood by the uninitiated without careful study.* There are portions of the subject that are rather simple and clear.

It will be noted that in the physiologic approach to this problem, the physiologist must resort to the use of surgical methods, without the successful use of which progress in this field could not occur.

It is best to approach this subject by outlining the periods and phases of gastric secretion. For the most part these are well established and recognized.

*The eighth E. Starr Judd Lecture, presented on Jan. 15, 1941, at the University of Minnesota Medical School, Minneapolis, Minn.

†Nathan Smith Davis Professor of Physiology and Pharmacology, Northwestern University Medical School, Chicago, Ill.

Received for publication, July 28, 1941.

PERIODS AND PHASES OF GASTRIC SECRETION

Gastric secretion may be divided into two periods:

Period I. The Period of Interdigestive or Continuous Secretion.—This is the secretion that occurs in the absence of food from the stomach.[1] Its amount and acidity vary. It is present in variable amounts throughout a fast of forty days.[2] Its existence was not recognized by Pavlov[3] because he thought the resting or empty stomach does not secrete acid, and that if acid is present, it is due to the thought of food. Yet, unless one recognizes that the empty stomach does secrete acid at periods, one will erroneously interpret the occurrence of a "spontaneous" secretion after the introduction of an experimental procedure as evidence of stimulation.

In experimental work on man and animal the continuous secretion should be collected for a period before any procedure is introduced, and the fact should be kept in mind that a small increase or decrease may be spontaneous. It is also important under certain conditions to observe the recovery of the secretory mechanism of the stomach after it has been stimulated. Sometimes after the stomach has emptied, it continues to secrete abnormal amounts of acid.

Some patients, particularly those with a duodenal ulcer, manifest a "hypernormal continuous secretion"; i.e., their stomachs continue to secrete a copious quantity of acid juice after they have emptied.[4] Although the volume of the secretion may be reduced by a relatively large dose of atropine, the secretion is not abolished as is the normal continuous secretion.[4a] This suggests that in such patients some abnormal process is concerned, or that some process which plays a minor role in the normal state has been activated. It is possible that histamine is being produced excessively by an irritated mucosa, since the secretory response to the ordinary doses of histamine used is not prevented by ordinary doses of atropine[5] (for atropine action, *vide infra*).

The nature of the stimuli which give rise to the continuous secretion of gastric juice is uncertain. The solution of the problem awaits a complete knowledge of the factors concerned in the secretory response of the stomach to a meal.

Period II. The Period of Digestive Secretion.—This is the secretion that occurs in response to a meal. For clarity and simplicity, *this period is divided into three phases,* the cephalic, the gastric, and the intestinal.[6] Each phase is named to denote the region in which the stimuli are acting to cause secretion. This assists in the analysis of the subject.

Phase 1. The Cephalic Phase. This phase denotes that the stimuli are acting in the region of the head.

The stimuli are the sight, smell, taste, and thought[7] of food and act *in the presence of appetite* through (A) *conditional reflexes* (the

"psychic" secretion of Pavlov), which are dependent on the integrity of the cerebrum, and by (B) *unconditional reflexes,* which are not dependent on the cerebrum. An unconditional reflex stimulation of gastric secretion is analogous to the unconditional secretion of saliva when acid is placed in the mouth. The conditional reflex stimulation of gastric secretion is analogous to the conditional secretion of saliva when a bell is rung, or when one thinks of food or sees food. Zeliony[8] has reported that decorticated dogs do not secrete in response to the sight and smell of food, but do respond when they are "sham fed." "Sham feeding" consists of feeding an animal with an esophagostomy; the masticated and swallowed food does not enter the stomach.

The vagi contain the excitatory nerves for the cephalic phase of gastric secretion; they also contain inhibitory nerves. The splanchnic nerves gastric secretion. They do not conduct any of the nerve impulses responsible for secretion in sham feeding. They may, however, conduct impulses which stimulate secretion under other conditions, though this has not been demonstrated.

TABLE I

AMOUNTS OF JUICE FOR EACH PHASE

PERIOD OR PHASE	DOG		MAN	
	NORMAL (C.C.)	ABNORMAL (C.C.)	NORMAL (C.C.)	ABNORMAL (C.C.)
Continuous	0.5-4/hr.	10-30/hr.	30-60/hr.	100-360/hr.
1. Cephalic	10-75/20 min.	500-700 in 4-6 hr.*	50-150/20 min.	?
2. Gastric phase	100-250/5 hr.		225-350/5 hr.	?
Mechanical	20-50/30 min.	?	?	?
Secretagogues	20-40/30 min.	?	?	?
Liver extract				
3. Intestinal phase	200-300/12 hr.	600-650/24 hr.†	225-350/5 hr.?	

*Sham feeding for 4 to 6 hours, exceptional cases. Maximum rate of secretion I have observed in man is 11 c.c. per minute. Maximum rate of secretion I have observed in dogs is 4 c.c. per minute.

†Pylorus blocked and feeding via duodenal fistula (Webster and Armour). We have obtained from 500 up to 1,500 c.c. of juice in 24 hours from enterectomized dogs, with gastric catheter and 400 c.c. Ringer's solution every 6 hours. Atropine markedly reduced (about two-thirds) the volume of secretion. Operations in the upper abdomen stimulate gastric secretion; why, is unknown. We believe it is a "traumatic secretion" due to absorption of secretagogues, such as histamine. It does not take much histamine to stimulate gastric secretion; much more is required to produce shock, a condition in which secretion of acid does not occur.

The amount of juice (Table I) resulting from the cephalic phase is subject to considerable variation in the same subject. This phase is prevented by atropine as well as by section of the vagi.

Some surgeons, when performing a partial gastrectomy for peptic ulcer, have sectioned one or both vagus nerves to annul the cephalic phase of gastric secretion. The value of the procedure in the treatment of ulcer is mooted.[9, 10, 11] The procedure will, if the vagi are completedly sectioned, annul the cephalic phase and reduce the total secretion of gastric juice in response to a meal. The efficacy of the vagotomy in the therapy of ulcer will depend on the extents to which the cephalic phase contributed to the patient's total gastric secretion, to which the

various branches of the vagi have been sectioned, and to which compensatory changes occur after vagotomy. *It should be remembered that vagotomy causes other changes than an annulment of the cephalic phase of gastric secretion.* Since vagotomy should decrease the total secretion of acid to a meal, it should have a favorable effect in preventing postoperative jejunal ulcer. However, vagotomy would have no effect on a secretion due to the production of histamine by an irritated gastric or intestinal mucosa, the likelihood of the occurrence of which would be diminished as the result of a decrease in the total production of acid in response to a meal. The section of the vagi decreases the tone of the gastric musculature at least temporarily, and retards permanently the rate at which solid or thick pasty foods are evacuated from the stomach. (a) This might tend to increase the gastric phase of secretion. (b) In addition, the vagotomy would prevent "acid inhibition" of the gastric phase from the intestine from occurring, at least to a large extent, and these two factors, (a) and (b), may compensate for the abolition of the cephalic phase and negate the advantage gained by the vagotomy. Further, if the vagi contain vasodilator nerves which oppose the vasoconstrictor nerves in the splanchnics, then vagotomy might favor a decrease in the blood supply of the gastric and intestinal mucosa. Thus, the physiologist is not surprised that the procedure of vagotomy in operations for ulcer is mooted. It is one of those biologic questions in which so many positive and negative factors may be concerned that the answer cannot be predicted. The question can only be answered by the study of clinical results and by the effect of vagotomy in animals that develop ulcer, such as Mann-Williamson dogs (gastrojejunostomy with the alkaline digestive juices diverted to the ileum).

PHASE 2. THE GASTRIC PHASE. This denotes that the stimuli are acting in the stomach.

Two types of stimulating agents applied to the stomach excite the parietal cells to secrete. They are: (A) *mechanical distention* and (B) *secretagogues,* or chemical substances of which there are two types: (1) those which are *naturally present in food,* e.g., lean meat, liver, and milk whey; and (2) those which *arise from the digestion of food,* such as split-protein products and possibly fatty acids.

Mechanical distention is the only adequate type of mechanical stimulus known. Rubbing the mucosa with a glass rod, a feather, or sand does not stimulate the secretion of acid.[3] Beaumont observed secretion in response to distention, as did Pavlov. Pavlov attributed it to a "psychic" response; the dog thought food was being placed into his stomach. But Pavlov did not cut the vagi to ascertain whether his interpretation was correct. Distention of the stomach with the vagi sectioned stimulates gastric secretion and hence the secretion cannot be "psychic" in origin (Fig. 1).

Secretagogues are naturally present in meat juice and certain other foods. Their presence can be demonstrated by perfusing meat juice through a pouch of the entire stomach with the vagi sectioned (Fig. 1). By this means any substance can be tested for "gastric secretagogues." We never use more than 50 c.c. of an aqueous solution of the substance in order to avoid stimulation by distention. For example, if the stomach is distended with 150 to 300 c.c. of water, it will secrete, but not if 50 c.c. of water is continually perfused through the stomach. A solution of egg white perfused through the stomach does not stimulate; but *if the egg white is digested* with HCl-pepsin, and then perfused, stimulation occurs. If the perfusion is continued for one-half hour, as in our tests for secretagogues, the stomach secretes during that period and continues to secrete above the control level for 1.5 hours and sometimes longer. Alcohol, 2 to 7 per cent, and histamine, 10 to 25 mg. in 50 c.c. of water, perfused through the stomach stimulates the secretion of acid.

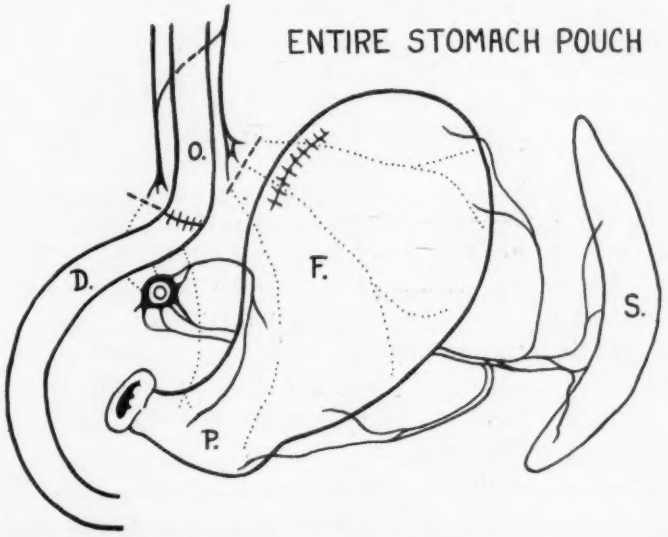


Fig. 1.—A pouch of the entire stomach. All the vagus branches are sectioned, with the possible exception of one that leaves the right vagus and passes to the celiac ganglion. However, such a pouch does not manifest a "psychic secretion." Secretion of such a pouch can be inhibited via the splanchnic nerves; there is no evidence that stimulation of acid production can occur via the splanchnic nerves. Distention of the pouch and perfusion with meat and liver extract and other solutions containing secretagogues stimulates acid production.

PHASE 3. THE INTESTINAL PHASE. This phase denotes that the stimuli are acting in the intestine.

(A) *Secretagogues,* or chemical substances, are the only type of stimuli which stimulate gastric secretion on application to the intestine.

Mild distention has no effect. Undue distention or irritation of the intestine at first inhibits gastric secretion, I believe, reflexly. If injury to the mucosa is produced, stimulation may result from the absorption of secretagogues, possibly histamine, produced locally.

Secretagogues which act in the stomach also act in the intestine. Numerous other substances[3, 12] applied to the intestine stimulate gastric secretion; for example, soaps, fatty acids, and peptone. Whether soaps are normally present in sufficient concentration to stimulate is conjectural. Neutral fat in the intestine inhibits gastric secretion (enterogastrone production). According to Shay and his associates,[13] sodium oleate (15 per cent) or soap depresses gastric secretion, which depression, as in the case of that due to olive oil and 40 per cent glucose, disappears after from 1.5 to 2.5 hours; then the secretion returns to normal or may go above the normal, as is also observed after suppression of secretion with atropine. This action of fat is one reason why, after the patient with ulcer has received milk and cream on the hour during the day, it is frequently necessary to do a "therapeutic aspiration" of the stomach at 11:00 P.M. to 2:00 A.M. That is, after the inhibition due to fat is over, the gastric secretion returns to a high rate. Another reason is that the administered alkali is absorbed as such and as NaCl along with water, and augments secretion as when Ringer's or Locke's solution is given by clysis. A possibility that should receive some consideration in explaining the stimulation of gastric secretion by alkalies is that the alkali in the intestine counteracts the "acid inhibition" of gastric secretion from the intestine (*vide infra*); this is entirely conjectural.

What Amount of Juice Is Produced as a Result of the Stimuli Acting in Each Phase?—A definite answer to this question cannot be given. Estimates are given in Table I. *Dog:* Those for the dog are fairly reliable and are based chiefly on my own observations. *Man:* Those for man on the continuous and cephalic secretion are based on my observations. Those for the gastric phase represent a guess. Those for the intestinal phase are based on Garbat's observations on duodenal feeding in ulcer patients. They may be abnormal.

A Consideration of Some Abnormal Conditions.—In the note under Table I, it is pointed out that operations in the upper abdomen are likely to cause a "hypercontinuous secretion." This we have observed many times. For example, after making a Pavlov pouch, the pouch may "hypersecrete" for a few days up to two weeks. It may occur after making a pouch of the entire stomach, especially if saline solution is given.[14] It is shown especially after total enterectomy in dogs, and it is most likely to occur when Ringer's or Locke's solution is given by clysis.[15] Some have seen it after converting a Pavlov pouch into a Heidenhain pouch, which sections the vagal innervation of the pouch, and have called it a "paralytic secretion."[3a] Several years ago, we[16] demonstrated how a "peptic ulcer" would enlarge after exposing it for photography, unless the postoperative hypersecretion was buffered by frequent feedings. This "hypercontinuous" secretion does not always occur; however, atropine definitely decreases, but does not abolish it.[15]

A partial obstruction of the pylorus should increase gastric secretion by prolonging the gastric phase. Whether such actually occurs will depend on the extent to which the obstruction excites mechanisms which inhibit secretion, such as reflex inhibition via the splanchnics or vagi, acid inhibition from acid in the stomach, and gastritis. The results of controlled experments show that partial pyloric obstruction increases gastric secretion in some animals.[17] It should, and usually does, increase the average acidity of the gastric contents (hypernormal acidity), because of the partial retention in the stomach of the acid secreted.

Resection of the pyloric portion of the stomach, although the pyloric mucosa does not secrete acid and pepsin, decreases the gastric phase of secretion.[18, 19, 19a] The pyloric portion of the stomach normally contributes to the gastric phase by increasing the effectiveness of secretagogues and distention (*vide infra*).[19] When the pyloric portion is excised, the remainder of the stomach secretes less acid when a secretagogue solution is applied. With the pyloric portion excised and the vagi sectioned above the diaphragm, very little secretion occurs when secretagogues are applied.[20] Thus, section of the vagi would abolish the cephalic phase and excision of the pyloric portion of the stomach would reduce the gastric phase. In such a stomach the secretion of acid in response to a meal would result chiefly from food acting in the intestine, or the intestinal phase; the amount of secretion should be markedly reduced unless the gastric remnant undergoes hypertrophy and hyperplasia, or the jejunal mucosa becomes irritated and produces histamine. If such a stomach empties rapidly, then much of the gastric juice formed from the intestinal phase would be buffered and neutralized only by the pancreatic juice, and bile and succus entericus. (An enteroenterostomy of the ascending and descending loops of jejunum, or an *en* Y or Roux operation by shunting the bile and pancreatic juice away from the gastroenterostomy predisposes to jejunal ulcer.)

Gastroenterostomy should affect only the gastric phase, provided it facilitates gastric evacuation. If the jejunum is overdistended by the food, then some reflex inhibition of secretion should occur. When performed for adequate reasons, it gives relief because (a) it tends to provide more "rest" to the ulcerated area, (b) the additional gastric orifice tends to diminish intragastric tension, (c) the average acidity of the contents tends to be diminished. The acidity of the gastric contents is diminished as a result (a) of improved gastric evacuation which decreases the gastric phase, (b) of improved enterogastric regurgitation, and (c) probably of secretory inhibitory reflexes from the jejunum. The operation fails chiefly because the jejunum is more sensitive to acid irritation than the duodenum and the gastric secretory mechanisms of the patient are too sensitive or "keyed at a high level," so the buffering and neutralizing action of the alkaline juices is not adequate to offset the susceptibility of the jejunal mucosa. The operation apparently yields better results in middle-aged and older patients,

particularly in the presence of some pyloric stenosis due to an old ulcer, than in younger patients, probably because of the declining gastric secretion due to age and the atrophic changes in the gastric mucosa associated with prolonged stenosis. The operation of pyloric occlusion with gastroenterostomy, which was designed to be applied to the younger group of patients and to simulate the anatomic condition of pyloric stenosis in the middle-aged, considered inadequately the physiologic factors concerned in gastric secretion, the regulation of gastric acidity and the susceptibility of the jejunal mucosa to acid-pepsin irritation. (A pyloric stump that cannot drain well is subject to mechanical factors which may cause distress.)

The important role that the alkaline juices play in the presence of a gastrojejunostomy is demonstrated by the Mann-Williamson dog, which develops a jejunal ulcer in almost 100 per cent of cases. In this operation the alkaline juices, except the locally produced succus entericus, are diverted to the lower ileum, so the acid chyme irritates the jejunal mucosa. The gastric acidity curve in response to a meal does not show the normal terminal decrease [16, 21, 22] and the stomach continues to secret for a longer period than normally. The gastric phase of secretion is probably increased due to the increased emptying time and in some animals the intestinal phase appears to be definitely prolonged. The volume of secretion is reduced, but not abolished by atropine, which suggests that the irritated mucosa is producing histamine.[5]

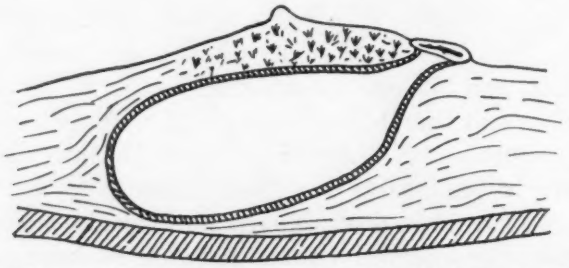


Fig. 2.—An autotransplant of the acid-secreting portion of the stomach made by the pedicle graft method. The pouch secretes when the animal is fed a meal. This is the crucial proof of the existence of a humoral mechanism for gastric secretion.

INHIBITION OF GASTRIC SECRETION

Nervous and humoral mechanisms are concerned in the inhibition of gastric secretion. *Nerves:* The splanchnic nerves and the vagi contain inhibitory fibers for gastric secretion, so mental states may inhibit secretion. Distention of the intestine inhibits secretion probably reflexly.

Enterogastrone.—Fat or concentrated sugar solution (10 per cent or above) introduced into the intestine inhibits gastric secretion. That the inhibition caused by fat is due to a chalone referred to as enterogastrone is clearly established. For example, the introduction of olive oil or cream into the intestine of a dog with an autotransplanted pouch (Fig. 2) inhibits the secretion of the pouch; whereas, the intravenous

administration of fatty chyle, soap, and properly emulsified fat does not. A highly purified extract of duodenal mucosa has been prepared which inhibits gastric secretion and motility when injected parenterally.[23] In man the inhibition caused by the introduction of 40 c.c. of olive oil into the duodenum lasts for from 1.5 to 2.5 hours.[13]

Acid Inhibition.—This expression is used to indicate that the presence of acid (0.2 to 0.4 per cent) in the stomach or intestine inhibits gastric secretion. Whether or not acid inhibition occurs depends on the nature and potency of the secretory stimulus. Thus, inhibition by acid is not observed under all conditions. Acid (0.36 per cent) in the stomach inhibits the action of secretagogues in the stomach (intragastric chemical phase), but not that of secretagogues in the intestine. Acid in the intestine inhibits the action of secretagogues in the stomach and in the intestine. When the secretory stimulus is strong, then acid in the intestine is less likely to inhibit, if at all. For example, when secretagogues are acting in the stomach and intestine simultaneously, acid in the intestine does not definitely inhibit. When gastric secretion is excited by histamine, acid in the intestine does not inhibit. The cephalic phase of gastric secretion is refractory to the inhibitory action of acid in the stomach or duodenum.[24, 25]

In view of the foregoing qualifications of acid inhibition of gastric secretion reported by Wilhelmj's[26] and Babkin's[25] laboratories, it is not surprising that the literature on acid inhibition is apparently contradictory. Some have observed it in man and others have not.[27-31] In the dog we[6, 12] found the effect of the introduction of acid into the duodenum to be uncertain.[31] To complicate the picture further, the continuous perfusion of acid (0.36 per cent) through a Thiry fistula of the duodenum and jejunum will usually after a latent period of about forty-five minutes cause a stimulation of gastric secretion.[12] This stimulation occurs after the mucosa has been injured with the acid. The feeding of a meal after such an experiment sometimes results in a hypernormal secretory response of a Pavlov pouch. Repeated daily perfusion of the Thiry fistula with acid for a period may cause a hypernormal continuous secretion.[12] It is possible that irritation of the intestinal mucosa with acid or any other agent releases histamine, or a histamine-like substance, as does irritation of the skin. This has to be considered in the interpretation of the secondary rise of gastric secretion when substances, such as 15 per cent sodium oleate, etc., are introduced into the intestine of man.[13]

Summarizing, a primary inhibition of gastric secretion from the intestine may occur as the result of enterogastrone liberation, reflex inhibition, or in the case of injury, the absorption of nonspecific inhibitory substances. A subsequent return of gastric secretion may be the result of escape of the stomach from inhibition due to the neutralization or disappearance of the inhibitory stimulating agent, or in the pres-

ence of irritation it may be due to the production of a histamine-like substance, which may give rise to a hypernormal response to a meal or to a hypercontinuous secretion.

THEORETICAL OUTLINE AND EVIDENCE REGARDING HOW PARIETAL CELLS MAY BE STIMULATED TO SECRETE BY VARIOUS STIMULI

The older literature on this subject has been reviewed by Babkin[3a, 31, 32] and by me.[33] Since then some progress has been made. The newer evidence will be presented with the pertinent older evidence in outline form with an attempt to distinguish between the known and unknown features of the problem.

1. *Extrinsic nerves,* as for example the secretory nerves in the vagi. The nerve impulses conducted by these nerves (a) may exert a direct secretory influence on the cell by releasing at their nerve endings acetyl choline or histamine, or by deplorization associated with the action potential which is associated with the "nerve impulse"; (b) may stimulate by causing vasodilation or a favorable vascular reaction for secretion; (c) may cause the production of a specific hormone, or a gastrin.

"Sham feeding," it is well known, does not cause a Heidenhain pouch (a pouch devoid of vagal innervation) to secrete. Hence, if the vagal secretory nerves stimulate the parietal cells by releasing a substance as postulated in *b* and *c* above, the substance acts only locally and does not pass into the circulation. Of the various possibilities, the local release of acetyl choline is most probable according to existing information.

2. *Mechanical distention,* as in the gastric phase. Mechanical distention may stimulate (a) by causing vasodilation and increased motility directly or through intrinsic nerves; (b) by stimulating intrinsic secretory nerves which release acetyl choline or histamine or excite the cells by the action potential; (c) by direct mechanical stimulation; (d) by producing a specific hormone, gastrin; or (e) by releasing histamine as the result of mechanical stimulation, since rubbing the skin may cause vasodilation by the *alleged* production of a histamine-like substance.

Evidence will be presented later which indicates that mechanical stimulation acts only locally. That is, mechanical stimulation of the main stomach does not cause a transplanted pouch to secrete.

3. *Secretagogues or chemical substances,* as in the gastric and intestinal phases. Secretagogues may stimulate (a) by being absorbed into the blood; (b) by producing a hormone, gastrin; (c) by stimulating intrinsic secretory nerves, as in mechanical distention; (d) or, as in the case of the stomach, by direct chemical contact with the parietal cell through local absorption or diffusion; (e) or, by causing vasodilation.

Evidence regarding how secretagogues act will be given later.

A hypothetical analysis such as this has to be made before a problem can be attacked experimentally. Such an analysis is frequently incomplete because of a deficiency in existing knowledge.

Does a Humoral Mechanism for Gastric Secretion Exist?—This question can be stated more simply as follows: When we eat a meal, does some agent enter the blood and cause the gastric glands to secrete?

This question can be answered affirmatively. When a meal not containing too much fat is fed, an autotransplanted pouch secretes (Fig. 2). This shows that a humoral mechanism is in part concerned in the gastric secretory response to a meal.[35] This observation also provides us with a method by which we can ascertain how various stimulating agents applied to the stomach or intestine stimulate gastric secretion.

The fact that an autotransplanted pouch secretes tells us nothing regarding the nature of the humoral agent.

What Is the Nature of the Humoral Agent?—The humoral agent (a) may be histamine; (b) may be a gastrin or a hormone different from histamine, or histamine-like; (c) may be secretagogues absorbed from the food in the stomach and intestine.

We have sought to answer this question by biochemical and physiologic methods. We first started out to identify the principle or the gastrin in acid extracts of pyloric mucosa.

A. Isolation of Histamine From Acid Extracts of Pyloric Mucosa.—Edkins and others showed that the subcutaneous injection of acid extracts of pyloric mucosa would stimulate gastric secretion. He called the active principle gastrin. He proposed a theory which maintained that the contact of food and acid with the pyloric mucosa caused a hormone, gastrin, to be formed, which was carried by the blood to the parietal cells. It was soon shown that a gastrin was present in extracts of fundic mucosa and of numerous other tissues. Since those tissue extracts which stimulated gastric secretion also depressed blood pressure like histamine, many believed that Edkins' gastrin was histamine, or a histamine-like substance.

Following the lead of Luckhardt, Koch, and Keeton, we undertook to isolate and identify the active principle. We[35] made the following observations. Acid extracts of the pyloric mucosa contain a substance which stimulates gastric secretion when given subcutaneously or intramuscularly. These extracts given intravenously rapidly depress blood pressure like histamine. The activity of the extracts is destroyed by histaminase. Histamine was isolated from such extracts as a crystalline sulfate and picrate. The secretory and vasodepressor activities, expressed as a ratio, found in the original extract, remained relatively constant in all fractions including the final step of crystallization. ***This evidence showed that Edkins' gastrin is histamine.*** However, the evidence does not warrant the conclusion that histamine is the gastric hormone. All that can be deduced is: either histamine is the gastric hormone, or there is no gastric hormone, or the true gastric hormone has not been extracted from gastric mucosa.

McIntosh[36] has studied the amount of histamine in the blood before and after feeding. He could not find a significant increase in blood

histamine after feeding. Neither did he find a significant increase in blood histamine after injecting 1 mg. subcutaneously. Thus, the parietal cells are more sensitive to histamine than the method for measuring the histamine in the blood. Histamine could be the humoral agent, because when it is injected very slowly intravenously it stimulates gastric secretion without causing vasodilation or a fall in blood pressure.[37] Since atropine (1 mg.) during the period of its maximum effect abolishes the secretory response to a meal in the dog, it is necessary to conclude that if histamine is a *normal* humoral agent atropine must prevent it from being formed.[37a]

B. Can Secretagogues on Being Absorbed Into the Blood Be the Humoral Agent?—Not being able to ascertain whether histamine is the humoral agent, we decided to ascertain whether secretagogues on entering the blood might be the humoral agent.

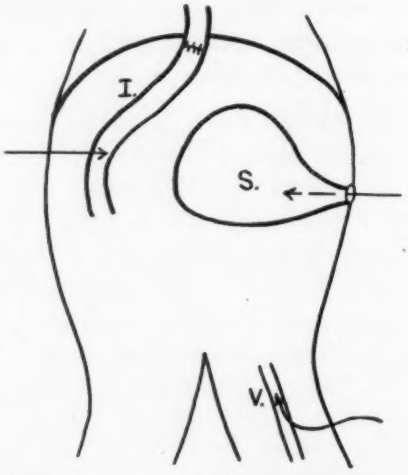


Fig. 3.—Analysis of stimulation of gastric secretion by secretagogues; 100 mg. of secretagogues applied to the stomach. *S* caused secretion; whereas, 400 mg. intravenously (*V*) was required. Liver extract introduced into the intestine (*I*) caused the pouch to secrete.

We[38] found that Lilly's preparation (No. 343) of the antipernicious anemia fraction of liver contained about 70 per cent of the secretagogues in liver. We freed this extract of vasodepressor material and injected it slowly intravenously. Gastric secretion was stimulated. This showed that *secretagogues could stimulate if they should be absorbed as such from* the intestine and stomach. We could not prove by chemical methods that secretagogues were absorbed from the stomach and intestine.

However, we made a "purified" preparation of secretagogues from liver extract and found that 400 mg. of this extract were required to stimulate when injected intravenously and only 100 mg. were required when applied to the stomach (Fig. 3). This result, which has been recently confirmed,[39] shows that *secretagogues applied to the gastric mucosa are more potent than secretagogues injected intravenously.*

This evidence, it may be argued, indicates the existence of a hormone mechanism for gastric secretion. Since secretagogues applied to the intestine or stomach cause a transplanted gastric pouch to secrete, secretory nerves are ruled out. Since 100 mg. of the liver extract applied to the stomach stimulated secretion and 400 mg. intravenously were required to stimulate, it is obvious that the 100 mg. applied to the stomach did not stimulate by being absorbed into the blood. Hence, it may be deduced that secretagogues applied to the stomach stimulate a transplanted pouch by causing the elaboration of a hormone. Such a deduction cannot be unequivocally accepted. The crucial experiment would be to use a dog with both a transplanted pouch and a pouch of the entire stomach, and then to apply to the latter an amount of "purified" secretagogues that would stimulate the transplant but would not stimulate the transplant when given slowly intravenously (*vide infra*).

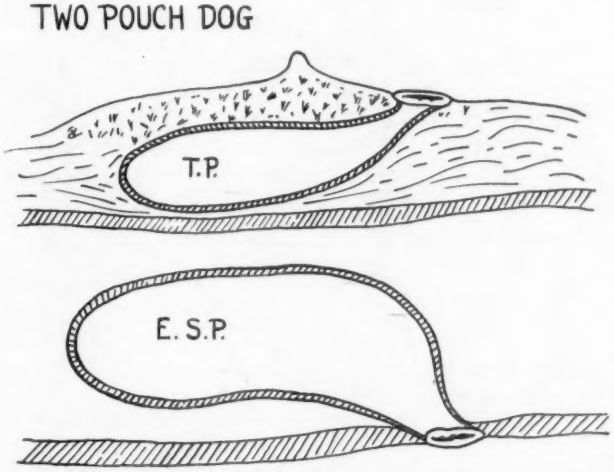


Fig. 4.—Analysis of the action of secretagogues when applied to the gastric mucosa. When liver extract is applied to the main pouch (*E.S.P.*), the transplanted pouch (*T.P.*) secretes.

Site of Origin of the Humoral Agent.—It is clear that a humoral mechanism for gastric secretion exists, because on feeding a dog with a transplanted pouch, the transplant secretes. This does not tell us whether the humoral agent comes from the stomach, or from the intestine.

The only way this question can be answered is to use a dog with a pouch of the entire stomach and with an autotransplanted pouch, or a "two-pouch" dog (Fig. 4). Then it would be possible to stimulate the stomach or the intestine and ascertain whether the transplant secretes. Secretion by the pouch can only be due to a humoral agent. (These studies[19] were made recently in our laboratory by Dr. R. A. Gregory.) The observations to date may be summarized as follows: (1) A humoral mechanism is *involved* in the action of *secretagogues* in the stomach. Perfusion of the entire stomach pouch (Fig. 4) causes the transplant

to secrete (4 dogs, numerous experiments). (2) A humoral mechanism is *involved* in the action of *secretagogues* in the intestine. On feeding the animal, which has an esophagoduodenal anastomosis (Fig. 5), the transplant secretes (4 dogs, numerous experiment). Application of liver extract to a Thiry fistula of the intestine (Fig. 5) causes the transplant to secrete (1 dog, 7 experiments). (3) A humoral mechanism is *not involved* in the action of mechanical distention. Distention of the main stomach (Fig. 5) does *not* cause the transplant to secrete (4 dogs, numerous experiments). (4) Distention of the transplant usually causes secretion.

Thus, the mechanism for mechanical and secretagogue stimulation of gastric secretion is not the same. Also, if a humoral agent is involved, it does not come from the parietal cell, because in both cases the parietal cells of the entire stomach pouch secrete.

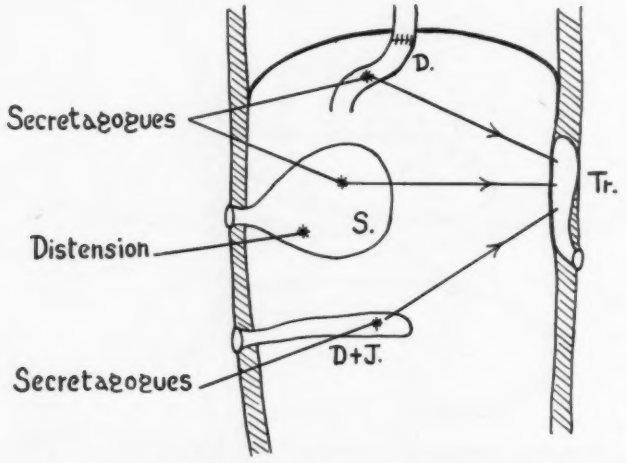


Fig. 5.—Secretagogues placed in the duodenum (*D*), the stomach (*S*). A Thiry fistula of the duodenum and jejunum (*D + J*) causes the transplant (*Tr.*) to secrete. Removal of the pyloric portion of the stomach (*S*) reduces the response to secretagogues and to distention. Distention of stomach (*S*) does not cause the transplant to secrete.

Site of Origin in the Stomach of the Humoral Agent Produced by Secretagogues.—A pouch of the "entire stomach" from which the pyloric portion of the stomach has been removed does not secrete as much acid in response to secretagogues as when the pyloric portion is intact.

To ascertain whether the pyloric portion of the stomach contributes to the humoral mechanism, we resected the pyloric antrum from a two-pouch dog (Fig. 4). After the resection of the antrum, application of secretagogues to the remainder of the stomach caused the transplant to secrete. However, less secretion was obtained than before antrectomy. Thus, the pyloric mucosa contributes to, but is not the sole origin of, the humoral mechanism obtained from the stomach.

Analysis of Local Stimulating Mechanism in the Stomach as Revealed by Use of Local Procaine Anesthesia.—Since the mechanism for the stimulation of secretion by distention and secretagogues is different, the

effect of local procaine anesthesia on the elicitation of the humoral mechanism was studied.[19]

A 5 per cent solution (50 c.c.) of procaine was perfused through the main stomach for fifteen to thirty minutes and then distention or secretagogue was applied. Procaine was also applied to the transplant, it having been found that procaine (25 c.c. of 5 per cent solution) injected subcutaneously had no effect on gastric secretion. Some of the results are shown in Table II. The results may be summarized as fol-

TABLE II

SECRETION OF TRANSPLANT GASTRIC POUCH ON PERFUSION OF POUCH OF ENTIRE STOMACH FOR 0.5 HR.*

PROCEDURE†	NO. OF EXPERIMENTS	MAIN POUCH‡			TRANSPLANT‡		
		VOL., 1.5 HR.	FA MG. HCl	TA MG. HCl	VOL., 1.5 HR.	FA MG. HCl	TA MG. HCl
Perfusion M. St. with L. E., with							
No procaine	22	9.3	9.2	36.2	2.0	2.0	3.0
Procaine to M. St.	12	3.5	0	12.7	1.3	0	0.7
Procaine to Tr.	10	5.5	4.7	24.6	1.9	1.6	2.3
Meal, mixed	4	22.8	17.6	32.9	6.9	2.8	6.3
Liver extract, 8 gm. No. 343	2	12.3	6.4	14.6	4.3	1.8	3.7
Meal (Procaine M. St.)	3	19.8	19.6	26.5	5.0	2.7	3.7
Liver extract M. St.	2	14.3	16.3	23.7	4.4	1.8	3.3
Distention (M. St.)	10	11.4	13.9	22.2	2.0	0	0.9
Distention + procaine	6	5.8	0	7.1	1.4	0	1.1
Perfusion 25 mg. histamine	6	6.4	42	55	2.4	3.2	5.7
Perfusion + procaine	3	7.1	29	41	3.3	5.6	7.4
Perfusion 2% alcohol	4	9.3	21	36	3.0	5.3	6.0
Perfusion + procaine	5	11.5	38	50	4.3	5.5	8.2

*Procaine 50 c.c. of 5 per cent solution for 15 to 30 minutes; 25 c.c. of 5 per cent procaine subcutaneously has no effect on response of pouch to perfusion.

†*L. E.* Liver extracts. *M. St.* Main stomach. *Tr.* Transplant.

‡The pouches were secreting no free acid when the experiments were performed.

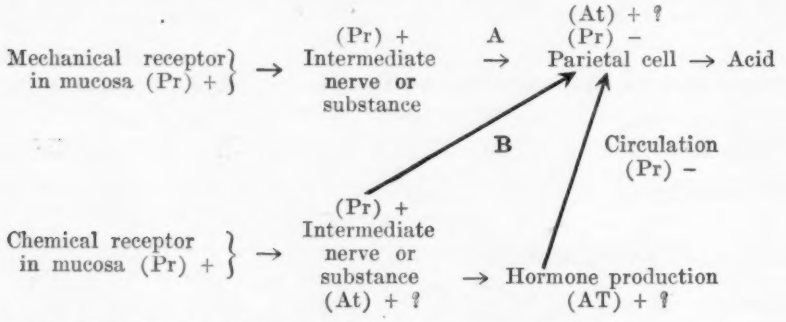
lows: (1) Procaine applied to the pouch of the entire stomach abolishes the response to distention and secretagogues. (2) Procaine applied to the pouch of the entire stomach prevents the transplant from secreting in response to secretagogues applied to the former. (3) The procainized transplant secretes when secretagogues are applied to the entire stomach pouch or to the intestine, or when a meal is fed. (4) Procaine applied to the entire stomach pouch does not prevent stimulation of both pouches on the application of histamine (10 to 25 mg. in 50 c.c. of water) or alcohol (50 c.c. of 2 to 7 per cent) to the pouch of the entire stomach.

Indirect evidence strongly indicates that alcohol stimulates gastric secretion by causing the liberation of histamine.[41] If histamine is the gastric hormone, then alcohol acts on a different point in the gastric secretory mechanism than secretagogues.

The procaine evidence shows: (a) that procaine does not act on the parietal cells (see *3* above); (b) that procaine probably does not act by preventing the absorption of secretagogues, since it is practically devoid of vascular action; (c) and that procaine most likely acts by block-

ing a local receptor mechanism (mechanical and chemical) which causes a local secretory response to mechanical stimulation and the liberation of a hormone on secretagogue stimulation. *Two types of receptors probably exist in the gastric mucosa:* one mechanically excitable, which does not release hormone, and another chemically excitable, which releases hormone. Alcohol probably acts directly to liberate histamine.

This concept can be illustrated by the following diagram:



A and *B* could involve either a secretory or a vasomotor reflex.

Atropine and procaine do not prevent histamine and alcohol stimulation, because histamine is absorbed and alcohol causes, by direct action, histamine formation.

Atropine prevents the action of secretagogues (liver extract) injected intravenously. It reduces, but does not prevent, the action of moderate amounts (0.5 mg.) of histamine, but in small amounts (0.2 to 0.3 mg.) does prevent histamine stimulation.

(*At*) + ? Atropine inhibits in adequate doses but the site of action is questionable.

Evidence Required to Settle Definitely Nature of Humoral Agent.—

1. To show that histamine is the hormone, some method more sensitive than those available will be required; or we will need to find some agent that will destroy histamine rapidly, and will at the same time stop a transplant from secreting. Histaminase acts slowly; it does not prevent injected histamine from acting; it does not reduce the gastric secretory response to a meal.

2. To rule out definitely the possibility that secretagogues act by being absorbed into the blood, it must be shown, for example, that 100 mg. of secretagogues applied to the stomach will stimulate a transplant, and that the same quantity intravenously will not. Or

3. To find some agent which will stimulate secretion in a transplant when applied to the entire stomach pouch, but which will not stimulate the transplant when given intravenously. Fatty acids and soaps are alleged to stimulate secretion when applied to the stomach but not when injected intravenously. But Gregory[19] found that soap confined to the stomach does not stimulate secretion.

4. To find some agent in the blood that stimulates, but is not a protein-split product resulting from absorption.

5. (A) One should probably search further for a gastrin that is not histamine. (B) One should isolate and identify the secretagogue or secretagogues in liver and meat extract.

Effect of Atropine.—In the dog the effect of atropine is well established. One milligram subcutaneously abolishes the normal continuous secretion and the gastric secretory response to a meal for from one to three hours. It abolishes all the phases of gastric secretion. The same dose produces a definite but limited inhibition of the response to histamine; the inhibition consists chiefly of a decreased volume output of acid without much change in acidity;[37a] the acidity may increase slightly.

The exact site of action of atropine is uncertain. It undoubtedly acts to block the action of secretory nerves. If histamine acts only on the parietal cells, then atropine probably acts also in part on the parietal cell.[42] Atropine does not abolish the secretory response to alcohol.[41] This indicates that alcohol releases histamine,[40] and, if histamine is a normal humoral agent, that alcohol releases histamine by a different mechanism (irritation) from that concerned in the release of histamine by secretagogues in food. This observation is of much interest in that it demonstrates the existence of a mechanism for gastric secretion that cannot be blocked by atropine. This would indicate that in man when a secretion is occurring that cannot be blocked for an hour or more by atropine histamine or a histamine-like substance is responsible.

In man atropine (1 or 2 mg.) abolished the *normal* continuous secretion but not that seen in some patients with duodenal ulcer. Its effect on the response to a meal is contradictory.[43] This is not surprising in view of the fact that in most studies patients with ulcers were used and the methods, stimulating agents, and dose of atropine and other factors are varied. (This subject deserves investigation in the light of recent knowledge.) Atropine decreases the volume output of acid in response to histamine,[45] and to alcohol, as in the dog.[4a] In patients with ulcers on hourly milk and cream diet atropine apparently only decreases the volume output of secretion[44] as in the dog with a jejunal ulcer;[5] it certainly does not abolish it as a rule. These observations constitute strong presumptive evidence that in patients with ulcer histamine or a histamine-like substance is produced. If those reported failures of atropine, in doses adequate to cause complete xerostomia and disturbances of vision, to abolish the gastric secretory response to a meal in man are not due to the presence of an ulcer or a "preulcer" condition, then normal men have a gastric secretory mechanism not found in the normal dog. Then man's predisposition to ulcer may be due to this tendency to produce histamine or a mechanism not readily blocked with atropine.

REFERENCES*

1. Carlson, A. J.: Physiol. Rev. 3: 1, 1923.
2. Hoelzel, F. A.: J. Physiol. 77: 166, 1926.
3. Pavlov, I. P.: The Work of the Digestive Glands, London, 1910, C. Griffin & Co.
3a. Babkin, B. P.: Die Aussere Sekretion der Verdauungsdrüsen, Berlin, 1928, Julius Springer.

*Only those references serving as an introduction to the literature are cited.

4. Bloomfield, A. L., Chen, C. K., and French, L. R.: J. Clin. Investigation **19:** 863, 1940.
4a. Keefer, C. S., and Bloomfield, A. L.: Arch. Int. Med. **38:** 303, 1926.
5. Ivy, A. C., and Bachrach, W. H.: Am. J. Digest. Dis. **7:** 76, 1940.
6. Lim, R. K. S., Ivy, A. C., and McCarthy, J. B.: Quart. J. Exper. Physiol. **15:** 13, 1925; **15:** 55, 1925.
7. Bloomfield, A. L.: Am. J. Digest. Dis. **7:** 205, 1940.
8. Zeliony, G. P.: Eleventh Internat. Physiol. Cong., Edinburgh, July, 1923.
9. Klein, E.: Ann. Surg. **90:** 65, 1929.
10. Best, R. R., and Orator, V.: Ann. Surg. **96:** 184, 1932.
11. Winkelstein, A., and Berg, A. A.: Am. J. Digest. Dis. **5:** 497, 1939.
12. Ivy, A. C., and McIlvain, G. B.: Am. J. Physiol. **67:** 124, 1923.
13. Shay, H., Gershon-Cohen, J., and Fels, S. S.: Ann. Int. Med. **13:** 294, 1939.
14. Dragstedt, L. R.: Am. J. Physiol. **90:** 331, 1929.
15. Gray, J. S., Wells, J. A., and Ivy, A. C.: In press.
16. Orndorff, J. R., Fauley, G. B., and Ivy, A. C.: Am. J. Digest. Dis. **3:** 26, 1936-1937.
17. Droegemueller, E. H., Meyer, J. L., and Ivy, A. C.: Arch. Int. Med. **40:** 434, 1927.
18. Wilhelmj, C. M., O'Brien, R. T., and Hill, F. C.: Am. J. Physiol. **116:** 685, 1936.
19. Gregory, R. A., and Ivy, A. C.: In press.
19a. Kim, M. S.: Mitteil. der Med. Akad. z. Kioto **12:** 731, 1934; **17:** 342, 1939.
20. Wilhelmj, C. M., McCarthy, H. H., and Hill, F. C.: Am. J. Physiol. **117:** 553, 1936.
21. Fauley, G. B., Ivy, A. C., Terry, L., and Bradley, W. B.: Am. J. Digest. Dis. **5:** 792, 1938-1939.
22. Wilhelmj, C. M., and Finegan, R. W.: Am. J. Digest. Dis. **5:** 373, 1938-1939.
23. Gray, J. S., Bradley, W. B., and Ivy, A. C.: Am. J. Physiol. **118:** 463, 1937.
24. Wilhelmj, C. M., McCarthy, H. H., and Hill, F. C.: Am. J. Physiol. **120:** 619, 1937.
25. Day, J. J., and Webster, D. R.: Am. J. Digest. Dis. **2:** 527, 1935.
26. Wilhelmj, C. M., Finegan, R., and Baca, D. E.: Am. J. Digest. Dis. **6:** 73, 1939.
27. Griffiths, W. J.: J. Physiol. **87:** 34, 1936.
28. Shay, H., Gershon-Cohen, J., and Fels, S. S.: Am. J. Digest. Dis. **6:** 361, 1939.
29. Apperby, F. L., and Norris, J. H.: J. Physiol. **70:** 158, 1930.
30. Welch, C. S., and Comfort, M. W.: J. Clin. Investigation **15:** 599, 1938.
31. Stevens, R. E., Segal, H. L., and Scott, W. J. M.: Am. J. Digest. Dis. **6:** 706, 1939.
32. Babkin, B. P.: J. Canad. M. A. **38:** 421, 1938; Am. J. Digest. Dis. **5:** 467, 1938-1939.
33. Ivy, A. C.: Physiol. Rev. **10:** 282, 1930.
34. Farrell, J. I., and Ivy, A. C.: Am. J. Physiol. **74:** 639, 1925.
35. Sacks, J., Ivy, A. C., Burgess, J. P., and Vandolah, J. E.: Am. J. Physiol. **101:** 331, 1932.
36. McIntosh, F. C.: Quart. J. Exper. Physiol. **28:** 87, 1938.
37. Ivy, A. C., and Javois, A. J.: Am. J. Physiol. **71:** 604, 1924-1925.
37a. Gray, J. S.: Am. J. Physiol. **120:** 657, 1937.
38. Kim, M. S., and Ivy, A. C.: Am. J. Physiol. **105:** 220, 1934.
39. Bucher, G., and Hands, A. P.: Unpublished.
40. Dragstedt, C. A., Gray, J. S., Lawton, A. H., and Ramirez, M. A.: Proc. Soc. Exper. Biol. & Med. **43:** 26, 1940.
41. Gray, J. S., and Bachrach, W. H.: Proc. Soc. Exper. Biol. & Med. **43:** 36, 1940.
42. Gray, J. S., and Ivy, A. C.: Am. J. Physiol. **120:** 705, 1937.
43. Klein, E.: Arch. Surg. **26:** 246, 1933.
44. Kirsner, J. B., and Palmer, W. L.: Am. J. Digest. Dis. **7:** 85, 1940.
45. Atkinson, A. J., and Ivy, A. C.: Am. J. Digest. Dis. **4:** 811, 1938.

THE MANAGEMENT OF GASTRIC RESECTION FOR THE "POOR RISK" PATIENT

H. McCorkle, M.D., and H. Glenn Bell, M.D., San Francisco, Calif.

(From the Department of Surgery, University of California Medical School, and the Surgical Service of the University of California at the San Francisco Hospital)

AT TIMES the surgeon attends a patient urgently in need of surgical treatment for chronic disease of the stomach, but in poor or even critical physical condition. Starvation, old age with cardiorenal and vascular changes, gastric retention with edema and atony of the wall, and infection of the gastric contents are some of the factors involved singly or in combination to make the patient a poor risk for difficult or prolonged operation on the stomach and for the postoperative complications that may arise. We have found certain measures recently employed in the handling of these poor risk patients to be especially worth while.

A period of hospitalization before operation is essential. This may occupy from six to fourteen days and occasionally a longer time is necessary. There has never been occasion to regret this delay in surgical treatment and usually we have been rewarded by improvement in the patient's general condition. Ample opportunity is provided for the establishment of proper water, protein, and electrolytic balance. When gastric retention is complete or almost so, this balance must be accomplished chiefly by the parenteral route. The administration of Ringer's solution replaces salts, and fluid in the form of glucose solution is also readily given. Records of the intake and output of fluid and frequent determinations of the blood chlorides are essential. The production of edema is carefully avoided. Transfusions of blood help to replenish low blood proteins and to aid in the restoration of lowered hemoglobin and erythrocyte levels. Plasma transfusions are also given when the blood proteins are low. Vitamins B and C are injected parenterally if not taken by mouth. During this period digitalization of the patient may be accomplished if cardiac decompensation is present. An attempt is made to ascertain the presence of renal insufficiency and to correct it if possible before operation.

Careful preparation of the stomach is important. When the gastric residue is large or obstruction of the stomach is complete and of long standing, the gastric content is almost always infected and the walls of the stomach are thickened, atonic, and edematous. Contamination of the operative field with the contents of such a stomach would invite sepsis, and suturing the walls would encourage disaster from leakage. The infection can be considerably reduced, the edema diminished, and

Received for publication, March 10, 1941.

the muscular tonus at least partly revived by proper preparation. Complete obstruction of the stomach requires lavage through a large stomach tube with a considerable amount of fluid in order to remove the larger particles that may be in the residue. Repetition at least once may be necessary. Often bits of undigested food and undissolved medicinal tablets are removed in this manner. A small nasal tube is then passed into the stomach and connected to the continuous suction apparatus. The patient maintains a continuous lavage by drinking clear fluids at frequent intervals, and this treatment is supplemented by periodic lavage carried out by the nursing or intern staff. Tap water is generally employed. The tube is clamped off and disconnected several times a day so that the patient may be up and about the ward or room. Having the patient out of bed for several periods during each day is an important part of his routine which should be maintained whenever possible. At meal times he is given a clear fluid diet, dilute meat broths, sweetened fluids, tea and jello (milk and unstrained orange juice will later obstruct the small tube and should not be given). The tube is clamped off during the meal and for the ensuing hour or two. This allows even the patient with obstruction to absorb some nutrition and gives him the satisfaction of taking something at meal time. Later, suction and lavage are resumed. In a few days the stomach becomes grossly clean and tends to return to a more normal size. The edema of the wall subsides and opportunity is afforded for it to regain some of its lost tonus. On the last day or two preceding operation, dilute hydrochloric acid in water may be given by mouth or used in the lavage for its supposed bacteriostatic action.

Objections to this rather strenuous "cleaning up" process might be raised on the ground that bleeding might be incited in the diseased stomach. In our experience this has not occurred whether the obstruction is caused by carcinoma or by ulcer. In the patients without obstruction, particularly those in whom severe hemorrhage has occurred, the regime described above is not fully carried out. It is not necessary if there is little or no residue in the stomach. Even for the unobstructed patients, however, the clear fluid diet is enforced for at least three or four days prior to operation, and lavage of the stomach is carried out for about forty-eight hours with the small indwelling tube and suction apparatus as described above. Dilute hydrochloric acid in tap water is given if gastric acidity is low, but it is omitted for patients with ulcer who have high acid readings. In all cases the last lavage is given on the evening before operation, but the suction is continued until the patient is called to the operating room. The nasal tube is left in the stomach during the operation and is allowed to drain by gravity or is attached to a suction device.

The choice of preoperative medication for the poor risk patient is of considerable importance. Large doses of sedative are avoided. Usually a dose of $\frac{1}{8}$ or $\frac{1}{6}$ gr. of morphine is given before the patient

goes to the operating room, and to this may be added $\frac{1}{200}$ gr. of scopolamine. In some of the elderly patients, a small dose of sodium phenobarbital may be given hypodermically instead of the morphine. A dose of sodium phenobarbital on the evening prior to operation will help insure a night of rest.

In these bad risk patients, partial or subtotal gastrectomy is performed entirely under local anesthesia. When this type of anesthetic is skillfully administered, it is possible to carry through a difficult and prolonged operative procedure with the deliberate precision necessary for the successful execution of the Halsted silk technique. In fact, the local anesthesia and the use of silk supplement each other in accomplishing the procedure, for the gentle handling of tissue helps to make the use of local anesthesia possible in gastric resection, and the use of local anesthesia makes possible the prolonged operating time necessary for carrying out the details of the Halsted method. Both factors are of considerable importance in bringing the debilitated patient successfully through gastric resection.

The use of local anesthesia for upper abdominal laparotomy and gastric resection has been described previously. Credit for the anterior splanchnic block is given to Braun, but Finsterer did much to further its recognition as an acceptable method of anesthesia in operations on the stomach. Recently Ogilvie, Allen, and Rienhoff have advocated its use. Pack, Devine, and others have also mentioned it.

Employment of local anesthesia in connection with the use of silk for gastric resection in poor risk patients appears to justify its description here in some detail. It is probably true that, even in the best hands, local anesthesia for some reason or other may fail to be satisfactory for this sort of operative work. In most cases, however, skill, thoroughness, and accuracy employed in the administration of the anesthetic solution will be rewarded by successful anesthesia. Novocain is usually employed in dilutions of 0.75 or 1 per cent and to each ounce 2 or 3 drops of adrenalin solution are added. Field block of the abdominal wall is preferable to direct infiltration. The skin is carefully prepared with soap, water, alcohol, ether, and tincture of merthiolate solution, and is suitably draped. The field is outlined with intracutaneous wheals beginning at the tip of the ensiform process and extending down the costal margins to points just lateral to the rectus sheath on either side. From these points the series of wheals is continued vertically downward along the lateral borders of the rectus sheaths on either side to points at or slightly below the level of the umbilicus. The two series of wheals are joined by extending them to or immediately below the umbilicus. Employing a somewhat longer needle, introduced through these wheals, the fascia is pierced at intervals of about 1 cm. for the entire circumference of the field and a few cubic centimeters of novocain solution is injected at each point of perforation. The injection is carried out with a hand syringe and the plunger

is carefully withdrawn before each injection in order to be certain that none of the solution enters a blood vessel. The tissues should not be flooded with excessive amounts of novocain solution. When the field block has been completed, the incision is developed. Recently we have come to prefer the midline epigastric incision in most of these cases, though the right or left muscle-splitting or the paramedian incision is used if, for any particular reason, one of them appears to be indicated. As soon as the peritoneum is exposed, it is infiltrated with novocain solution over a fair-sized area and incised in one place. Further incision of the peritoneum is preceded by injection with novocain solution, which is carried back for a distance of about 3 or 4 inches on either side of the incision. Small retractors are then inserted. Exposure is gained with the utmost care and gentleness.

At this point an attempt may be made to decide by inspection whether the lesion is operable, or whether further manipulation is necessary before resectability can be determined. Before any considerable intra-abdominal manipulation is carried out, the splanchnic region is infiltrated with novocain, following essentially the method of Braun. A needle is inserted into the retroperitoneal space below the left lobe of the liver, to the right of the abdominal aorta, at or about the level of the celiac axis. The needle is inserted until it is felt to impinge upon the body of the first lumbar vertebra and then is withdrawn slightly. From 40 to 75 c.c. of the novocain-adrenalin solution is introduced slowly with due care to prevent intravascular injection. Operability is then confirmed by palpation which is facilitated by an exploration into the lesser sac if necessary. All intra-abdominal manipulations must be carried out with great care and the softest possible touch. No pain should be inflicted upon the patient at any time as it will cause him to strain, contracting the musculature of the abdominal wall and pushing the intra-abdominal viscera out into the operative field. Such a catastrophe demands the supplemental use of general anesthesia. It can be prevented in almost every case by the accurate placement of the local anesthetic and by care and gentleness in operative manipulations. Extensive subtotal gastrectomies have been done entirely under local anesthesia in this manner, but total gastrectomy has required the use of general anesthesia.

Silk (Halsted technique) has been used for several years in this clinic for general surgical work. It has proved to be admirably adapted to gastric surgery and particularly to these cases of gastric resection done under local anesthesia. The essential steps of the present method as applied to gastric resection are: The attachments along the greater and lesser curvatures are divided by sharp dissection, the vessels being clamped with fine pointed hemostats before division and immediately tied with fine silk ligatures. In malignant disease, the lesser and greater omenta are widely excised, together with the greater part of the stomach. If resection is indicated for a benign ulcer, the omental attach-

ments are divided close to the stomach and, generally speaking, a high partial or subtotal gastric resection is done. If the benignancy of the lesion is doubtful, it is managed as though it were malignant. In high resections it is occasionally necessary to use additional novocain solution to infiltrate the lesser omentum near the cardia of the stomach. Particular care must be taken not to perforate a vessel in this region because hematomas form very rapidly and are difficult to control. If the duodenum must be mobilized, it is sometimes necessary to inject novocain solution just to the right of the duodenal attachment before beginning the incision in the posterior parietal peritonum. The duodenum is divided between clamps with the electroscalpel. The fat is carefully removed from the proposed site of inversion, the duodenal stump is turned in with a Parker-Kerr inverting suture of treated gastrointestinal catgut (small caliber) and is further turned in with interrupted mattress sutures of fine silk placed with straight cambric needles or with very fine French-eyed needles. The silk sutures are placed about ⅛ inch apart and are tied just tightly enough to appose the tissues firmly without cutting or producing strangulation. These are further protected by neighboring omental tabs. Further division of the attachments along the greater and lesser curvatures by the method described above is continued until the level selected for division of the fundus is reached. The fat is removed from the greater and lesser curvatures at this site. The nasal tube is withdrawn by an attendant until its tip can be felt in the fundus above the proposed site of amputation. As a rule clamps are not employed in the amputation of the fundus; we prefer to depend upon the thorough preparation of the stomach, careful walling off of the operative field with suitable packs, and the use of suction in the open viscus to prevent contamination. In practice these methods have proved very satisfactory in the prevention of sepsis and the advantage of obtaining direct hemostasis in the open stomach is evident.

Infiltration of the base of the transverse mesocolon from within the lesser peritoneal cavity renders its manipulation painless, in case the splanchnic block has worn off or has not included this area. An incision is made in the transverse mesocolon through an avascular area near its base and to the left of the middle colic vessels. A loop of small intestine just distal to Treitz' ligament is brought through the opening in the transverse mesocolon to make the retrocolic anastomosis. Usually the retrocolic Reichel-Polya type of repair is used following gastric resection. In the very high resections in which the mesocolon cannot be sutured to the gastric stump, Treitz' ligament is divided (as described by Lahey) by extending the incision in the transverse mesocolon downward. This permits the exit of only the descending loop of jejunum through the opening in the transverse mesocolon which is later closed around the single descending loop of jejunum. Before dividing the fundus of the stomach, the loop of jejunum that has been

brought through the opening in the transverse mesocolon is sutured to the posterior wall of the stomach, above the proposed line of division, with interrupted sutures of fine silk placed about ⅛ inch apart with fine cambric needles. The distal end of the jejunal loop is at the greater curvature and the proximal loop at the lesser curvature of the stomach. It is important that the sutures be placed accurately and that the submucosa be included in each stitch (as described by Halsted). The sutures must be tied with care so that the parts are firmly apposed but are not cut or strangulated. Continuous sutures of silk are never used. When the posterior line of silk sutures has been placed and tied, incisions are made with the electroscalpel down to the submucosa in the anterior and posterior walls of the stomach, at the proposed site of amputation. This brings the vessels into view and the larger ones are ligated with fine silk ties passed on cambric needles while the smaller vessels can be safely coagulated with the electroscalpel. A small opening is then made into the lumen of the stomach and all fluid is aspirated by suction. The stomach is amputated by completing the incisions with the electroscalpel through the mucosa on all sides, and the specimen of the stomach containing the lesion is removed from the operative field. When this is done carefully, there is no spilling of gastric content. In addition, the field is always blocked off with drapes to prevent accidental contamination. An incision with the electroscalpel is made in the loop of jejunum parallel to the opening in the stomach and hemostasis and prevention of soiling are carried out as described in the technique of opening the wall of the stomach. A second posterior line of sutures, consisting of a continuous gastrointestinal catgut hemostatic suture, is placed through all the layers of the posterior aspect of the gastrojejunal stoma and is completed anteriorly as a Connell type of suture. The anterior line of sutures is completed by the introduction of Halsted mattress sutures of fine silk passed on fine cambric needles and is further reinforced with interrupted sutures of the same material, thus completing the anastomosis. All laparotomy pads are removed from the operative field and the gloves of the surgeon and all assistants are changed. Fresh towels are draped about the field and the abdominal wound and peritoneum are reinfiltrated with local anesthetic. The opening in the transverse mesocolon is then sutured with interrupted sutures of fine silk, around the gastric stump, or it is closed and fixed around the descending loop of the jejunum if the amputation has been very high and division of Treitz' ligament has been carried out. Final inspection for hemostasis and the security of closure of the duodenal stump is made before the closure of the abdominal wound is begun. The laparotomy wound may be closed in layers with interrupted silk sutures or with heavy dermal retention sutures placed about 2 cm. apart through all layers. The wound is dressed with gauze and adhesive strapping applied in such a manner that it will not interfere with movements of the lower thorax in deep respiration.

When performed in the manner described, gastric resection often requires from four to five hours, and in very difficult cases as long as six hours has been needed. In this length of time it is usually necessary to reanesthetize the splanchnic area and the abdominal wall, and this should be done as soon as the patient complains of the slightest discomfort. Aside from a transient drop in blood pressure which may occur if the local anesthetic is introduced rapidly in large quantities, the general condition of the patient usually remains essentially unaltered throughout the procedure. If the patient becomes restless at the end of three or four hours, a small dose of morphine or of sodium luminal may be repeated. It is gratifying to see the "bad risk" patient appear so well at the end of the long operation and to realize that the utmost has been accomplished to relieve him with the least risk to his precarious hold on life. It is a great satisfaction also to know that the intra-abdominal operative work has been deliberately and thoroughly done.

The patient is returned to his bed in the semi-Fowler position, but is moved frequently (at least every two hours). Inhalations of carbon dioxide-oxygen are given at intervals to promote deep respirations. Patients in their late sixties and seventies are assisted to sit on the edge of the bed twice daily beginning the first postoperative day, and on several occasions these elderly patients have been allowed to sit in a chair at the bedside for a short period each day, very soon after operation.

The nasal tube is connected to the suction device as soon as the patient is returned to his room. Continuous gastric aspiration is maintained, usually for forty-eight hours, but irrigation is forbidden. The patient is allowed nothing by mouth for the first seventy-two hours, but is encouraged to rinse his mouth, and the nurse is required to carry out oral hygiene at frequent intervals. Fluid balance is maintained by the parenteral route for the first few days, care being taken not to overload the cardiovascular system and to avoid edema. Blood transfusion is done if the patient does not appear to be progressing favorably, but it is not always required. An enema is ordered on the morning of the third day after operation. On the third day 1 ounce of water is given by mouth every two hours. On the fourth day this is increased to 2 ounces every two hours, alternating water with albumin water. On the fifth day, when progress is favorable, clear fluids (tea, broth, coffee, jello) are given in amounts up to 3 ounces not oftener than every three hours. No milk or fruit juice is given. On the morning of the sixth day a coddled egg is added and that evening a small baked potato is allowed. Beginning on the seventh postoperative day, the diet is very gradually increased by adding thin gruels and other bland foods. It must be remembered that the gastric capacity is much diminished and the feedings should be correspondingly small at first.

TABLE I

TABULATION OF CASES

CASE NO.	AGE YR.	CONDITION	PERIOD OF PREPARATION	LESION	OPERATION	OPERATIVE COURSE	CONVALESCENCE
1	74	Weak, fat, flabby, auricular fibrillation	1 wk.	Carcinoma of antrum of stomach	Gastric resection, distal three-fourths of stomach; Reichel-Polya repair, 4 hr. 10 min.	Pulse 64 to 112; B.P. 106/80, 96/64, 100/70; pressure dropped slightly during administration of splanchnic anesthetic	Uneventful; highest temperature 99.8° F.
2	51	Starved, emaciated, weak; loss of 49 lb. in 11 wk.	10 days	Carcinoma of stomach with complete pyloric obstruction	Gastric resection, distal three-fourths of stomach; Reichel-Polya repair, 4 hr. 15 min.	Pulse 72 to 108; B.P. 110/70 to 150/90	Uneventful; highest temperature 101° F. on day of operation; afebrile thereafter
3	49	Intractable pain from ulcer, 18 mo.; starvation, dehydration, emaciation, weakness	2 wk.	Large benign gastric ulcer; lesser curvature of stomach	Gastric resection, distal four-fifths of stomach; Reichel-Polya repair, 4 hr. 5 min.	Pulse 50 to 70; B.P. 96/70 to 130/70	Transfusion reaction; temperature 103° F., third postoperative day, then uneventful
4	57	Gastrointestinal bleeding, pyloric obstruction; vomiting, dehydration, weakness	1 wk.	Prepyloric carcinomatous ulcer, complete obstruction	Gastric resection, distal three-fourths of stomach; Reichel-Polya repair, 4 hr. 30 min.	Pulse 76 to 100; B.P. 122/74 to 140/74	Uneventful; highest temperature 101° F. day of operation; afebrile thereafter

5	74	Weak, anemic, senile; vomiting for 6 wk.	1 wk.	Carcinoma of gastric antrum, fixation and obstruction; 20% gastric residue at 6 hr.	Gastric resection, distal three-fourths of stomach; Billroth II repair, 4 hr. 45 min.	Pulse 52 to 80; B.P. 130/70, 74/44, 126/70; pressure dropped sharply during administration of splanchnic anesthetic	Temperature to 101.8° until fourth postoperative day, then afebrile; obstruction at gastroenterostomy stoma, tenth to seventeenth postoperative day; uneventful thereafter
6	48	Gastroenterostomy 7 yr. previously; anorexia, pain, diarrhea, loss of 40 lb. 2 yr. before entry	3 wk.	Large carcinoma of the stomach, greater curvature above stoma of gastroenterostomy	Gastric resection, five sixths fundus; resection and anastomosis of jejunum; Reichel-Polya repair, 5 hr. 55 min.	Pulse 80 to 112; B.P. 106/60, 90/60, 110/70; pressure dropped slightly during administration of splanchnic anesthetic	Signs of atelectasis and fever to 101.6° F. on fifth and sixth postoperative days; afebrile thereafter
7	52	Duodenal ulcer 15 yr.; gastroenterostomy 10 yr., without benefit; severe pain 1½ mo.; emaciated, very weak	3 days	Jejunal ulceration near gastroenterostomy site	Resection, end-to-end anastomosis, resection distal three-fourths of fundus of stomach; Reichel-Polya repair, 6 hr. 10 min.	Pulse 120 at start; 80 to 100 during operation; B.P. 112/86, 80/60, 106/60; pressure dropped during administration of splanchnic anesthetic	Atelectasis and pneumonia; died seventh postoperative day
8	63	Massive gastric hemorrhage, pyloric obstruction, anemia, hemoglobin 20%	7 wk.	Penetrating duodenal ulcer with pyloric obstruction and hemorrhage	Resection, three-fourths fundus of stomach; Reichel-Polya repair, 5 hr. 55 min.	Pulse 72 to 88; B.P. 102/70, 90/70, 110/80; pressure dropped slightly during administration of splanchnic anesthetic	Atelectasis first postoperative day; temperature 103.8° F., gradually subsided; uneventful after fifth day

TABLE I—CONT'D

CASE NO.	AGE YR.	CONDITION	PERIOD OF PREPARATION	LESION	OPERATION	OPERATIVE COURSE	CONVALESCENCE
9	75	Epigastric pain 1 yr.; weak, senile, anemic, hemoglobin 34%; loss of 15 lb.	15 days	Annular constricting lesion, antrum of stomach; one large metastatic nodule in lesser omentum; 10% gastric residue, 6 hr.	Resection, distal four-fifths of stomach; Reichel-Polya repair, 3 hr. 40 min.	Pulse 60 to 100; B.P. 110/60 to 130/80	Uneventful; highest temperature 100° F., rectally
10	66	Indigestion, epigastric pain, loss of 15 lb. in 4 mo.; thin, emaciated, anemic	10 days	Annular constricting ulcerative carcinoma in antrum of stomach, complete obstruction	Resection, five-sixths of stomach; Polya-Balfour anastomosis, 4 hr. 35 min.	Pulse 60 to 90; B.P. 110/60, 90/50, 120/60; pressure dropped slightly during administration of splanchnic anesthetic	Temperature 100.6° F. rectally second postoperative day; afebrile thereafter
11	39	Penetrating duodenal ulcer with hemorrhage, intractable pain, rheumatic heart disease, mitral stenosis and insufficiency: cardiac decompensation on several occasions in past	10 days	Duodenal ulcer penetrating into pancreas, with hemorrhage	Gastric resection, distal three-fourths of stomach including duodenal ulcer; Reichel-Polya repair, 4 hr. 50 min.	Pulse 90 to 110; B.P. 90/64, 76/50, 120/70; pressure low at start, dropped slightly after anesthetic given; rose toward end of operation	Pulmonary atelectasis third postoperative day; temperature 103.4° F.; uneventful after that episode

12	60	Epigastric pain, vomiting, 5 mo.; loss of 30 lb.; starved, emaciated, dehydrated, anemic	12 days	Prepyloric ulcerative, constricting carcinoma with obstruction	Resection, distal three-fourths of stomach; large ulcer crater extended into the head of pancreas; Reichel-Polya repair, 4 hr. 30 min.	Pulse 70 to 100; B.P. 112/68 to 130/75	Satisfactory 5 days; temperature to 102° rectally sixth day; peritonitis developed eighth day; patient died ninth postoperative day; autopsy: acute hemorrhagic pancreatitis with peritonitis; no gastrointestinal leakage
13	53	Penetrating duodenal ulcer, complete pyloric obstruction, hemorrhage, severe pain; several large hemorrhages under medical regime; emaciated, weak, very anemic	6 wk.	Large duodenal ulcer penetrating into the pancreas; complete obstruction and hemorrhage	Devine exclusion operation; resection, three-fourths stomach; Reichel-Polya repair, 4 hr. 5 min.	Pulse 120 at start; later 72 to 84; B.P. 130/70, 70/50, 100/64; pressure dropped during second splanchnic infiltration	Uneventful; highest temperature 99.4° F., rectally; afebrile
14	72	Starved, anemic, dehydrated, emaciated, delirious (pellagra), complete gastric obstruction	5 wk.	Benign ulcer, gastric antrum, penetration into pancreas; obstruction	Resection, distal four-fifths of stomach; Reichel-Polya repair, 6 hr. 15 min.	Pulse 60 to 112 during most of operation; last hour, 120; B.P. 156/84; 70/50 for short time following injection of splanchnic area; 140/70 at end of operation	Uneventful except for infection of abdominal wound with rise of temperature to 102° F.

It is important not to depress these patients by sedation in the postoperative period. When the operative work has been done carefully and with little trauma the patient usually has very little discomfort after his operation and ½ gr. of codeine at required intervals ordinarily is enough to keep him comfortable. If not, a single small dose of sodium phenobarbital will probably not depress him too much and will help to insure rest. Morphine is rarely required and seldom given to these patients after operation.

We usually leave the sutures in place for from fourteen to sixteen days in these feeble patients. It has also been found desirable to keep them in the hospital for several days longer than the younger or stronger patients.

On the University of California Service at the San Francisco Hospital, during the past year, we have had fourteen patients whom we considered to be "poor risks." The tabulation of cases appended (Table I) shows in brief the type of patient to whom our regime has been applied and the immediate result accomplished. These cases were selected because operation upon the stomach was essential. All patients were especially prepared and were operated upon entirely under local anesthesia. In each case three-quarters or more of the stomach was resected.

SUMMARY

Certain measures employed in the management of patients with gastric lesions previously considered inoperable because of the poor condition of these patients have increased the number of operations successfully performed. Chief among these are:

1. A period of hospitalization before operation for preparation which includes the treatment of hypoproteinemia, the correction of fluid and electrolyte balance, the administration of vitamins, the treatment of cardiac decompensation, and the detection and correction of renal insufficiency wherever possible.

2. Thorough mechanical cleansing and decompression of the stomach by means of gastric lavage and aspiration.

3. The use of local anesthesia and silk technique. The method as applied in the performance of gastric resection in the "poor risk" case is described. Accuracy and thoroughness in the placement of the anesthetic agent and gentleness, deliberation, and care in the operative manipulations are necessary for the accomplishment of gastrectomy under these conditions.

4. Careful supervision of the postoperative care of "poor risk" patients. Such details include provision for pulmonary ventilation, frequent changes in the patient's position, the regulation of the intake of fluids, feeding, and the limitation of narcosis.

HEMANGIOMA OF THE STOMACH

Review of the Literature and Report of Two Cases

Charles Bruce Morton, M.D., and Ray Edward Burger, M.D.
University, Va.
(From the Department of Surgery and Gynecology, University of Virginia School of Medicine)

BECAUSE of the very small number of hemangiomas of the stomach recorded in the literature, two additional cases seemed worth reporting, especially in view of the fact that one of them had been the subject of a preoperative gastroscopic examination, a procedure apparently never before performed in the previously recorded cases. A review of the literature indicated the rarity of gastric hemangioma not only as compared with the frequency of hemangioma in other tissues, but also as compared with the incidence of other types of benign tumors of the stomach.

Hemangiomas are common, most are benign, and most occur on the body surface. A small number involve the viscera; and yet a smaller number involve the bone, muscle, and central nervous system. Geschickter[5] reported 570 instances of hemangioma from the Johns Hopkins Hospital: 370 peripheral, 135 visceral, and 65 of bone, muscle, and the central nervous system. The majority of the visceral hemangiomas, 109 or 81 per cent, involved the liver. The remaining 19 per cent involved the heart valves and other internal organs including the mesentery, kidney, and gastrointestinal tract. None of these tumors, however, involved the stomach.[6]

Benign tumors of the stomach, which are much less frequent than malignant growths of the organ, include adenomas, polyps, adenomyomas, leiomyomas, fibromas, lipomas, neurofibromas, dermoid and echinococcus cysts, embryonic rests of the pancreas, osteomas, and hemangiomas. In Eiselsberg's Clinic[2] only 5 benign tumors were found among 1,125 gastric neoplasms, an incidence of 0.44 per cent. Eusterman and Senty[4] estimated from cases at the Mayo Clinic that only 1.3 per cent of all tumors of the stomach treated surgically are benign. Hillstrom,[8] reviewing records of the Department of Pathology of the University of Minnesota, found about 5 per cent of all tumors removed at operation or discovered at necropsy were benign. Stewart,[22] in 11,000 post-mortem examinations, found benign tumors of the stomach in 15 per cent. Rigler and Erickson[18] found benign tumors in 26 per cent of

Received for publication, March 18, 1941.

all gastric neoplasms at necropsy. In 1925 Eliason and Wright[3] collected 560 previously reported cases of benign tumors of the stomach and added 50 of their own, making a total of 610 cases. In 1932 Lockwood[12] recorded 4.5 per cent of gastric neoplasms benign, and stated that about 1,000 cases of benign gastric tumors had been reported. Since then many more have been recorded. Thus the incidence of benign tumor of the stomach has been reported variously from 0.44 per cent to 26 per cent of all gastric neoplasms. The number found at operation is much smaller than at necropsy, and few give rise to many symptoms.

The first recorded case of hemangioma of the stomach was reported by Lammers[10] in 1893. Since then cases have been reported by Stockis,[23] Guisez,[7] Burty,[1] Sherril and Graves,[20] Lemon,[11] Konjetzny,[9] Eusterman and Senty,[4] Moore,[14, 15] Siebner,[21] and Minnes and Geschickter.[13] In 1920 Lemon collected the first 5 cases from the literature and added 1. In 1925 Eliason and Wright collected a total of 10 from the literature in citing 610 cases of benign tumors of the stomach. Minnes and Geschickter in 1936 gathered 961 benign tumors of the stomach from the literature, of which 15 (1.6 per cent) were hemangiomas. They add a case of their own, believing it to make a total of 16. In a careful search of the literature, taking into consideration double and triple reporting of cases, we have been able to find only 12 different cases recorded.

TABLE I

CASES OF HEMANGIOMA OF THE STOMACH*

CASE	AUTHOR	YEAR	DETERMINATION AT
1	Lammers	1893	Necropsy
2	Stockis	1904-5	Necropsy
3	Burty	1914	Operation
4	Sherril and Graves	1915	Operation
5	Lemon	1920	Operation
6	Konjetzny	1921	Not stated
7	Eusterman and Senty	1922	Operation
8	Eusterman and Senty	1922	Operation
9	Eusterman and Senty	1922	Operation
10	Moore	1924	Operation
11	Siebner	1933	Operation
12	Minnes and Geschickter	1936	Necropsy
13	Morton and Burger	1941	Operation
14	Morton and Burger	1941	Operation

*A case reported by Guisez has been included in the tabulations of previous authors but has been excluded from our tabulation because, on reading the original report, it appears that this lesion was esophageal rather than gastric. It was visualized through the esophagoscope at the "cardia."

The pathologic characteristics of hemangioma of the stomach do not differ from those which might be expected. Hemangioma is a true neoplastic process involving vascular tissue and is believed to arise from embryonic rests of mesodermal tissue. The types encountered in the stomach appear to have been capillary and cavernous. They are usually round, soft, smooth, and with some semblance of a capsule, though some are diffuse. Some are on a pedicle, though most are interstitial.

They lie between the mucosa and serosa and are bluish black or reddish in color. To palpation they often feel "like a mass of angleworms." They occur at varying ages, ulcerate easily, and hemorrhage is a frequent symptom.

In general the symptoms are due to ulceration, hemorrhage, disturbance of gastric function, or malignant change. The case of Burty revealed sarcomatous change. They usually produce a filling defect on roentgenologic examination and are diagnosed as benign or malignant tumors. As far as can be ascertained, no previously reported case has been subjected to gastroscopic examination. In this connection, however, Schindler[19] said: "Benign tumors of the stomach are by no means rare. In my experience they have been found in 1.5 to 2 per cent of all the cases gastroscoped. . . . Angiomas are so rare that it will probably be a long time before one is seen gastroscopically, but they should be easily diagnosed."

CASE REPORTS

CASE 1.—R. C. (Hist. No. 157373), a white man, aged 36 years, was admitted to the Medical Clinic of the University of Virginia Hospital April 9, 1940. He complained of discomfort in the epigastrium of one year's duration. He had first noticed the discomfort in the early morning and usually it had been relieved by food, soda, or exercise, and had not returned during the day, if the patient had been moderately active. It had returned, however, when he had become fatigued. The discomfort had remained as a dull, gnawing, nonradiating type of mild pain throughout the year, and had not been associated with nausea, vomiting, anorexia, hematemesis, melena, or weight loss. His past and family histories were irrelevant except that a paternal uncle had had "ulcers of the stomach."

Physical examination revealed a well-developed and nourished white man who appeared to be in good health. No physical abnormalities were discovered. His abdomen seemed entirely normal. His temperature, pulse and respiratory rates, and blood pressure were within the normal range. Laboratory examinations, including various studies of the blood, urine, and gastrointestinal tract content, likewise revealed no abnormalities.

Roentgenologic Examination.—The gastrointestinal tract was examined roentgenologically after ingestion of a barium meal on two occasions, six days apart. Both examinations revealed an organic lesion, a ragged area on the lesser curvature of the stomach beginning at the level of the cardiac orifice and extending downward for 6.5 cm. There was also slight spasm at the pylorus, but the remainder of the stomach and duodenum appeared normal. The six- and twenty-four-hour interval examinations of the remainder of the gastrointestinal tract revealed no other abnormality. The roentgenologist believed that a malignant tumor might be present in the stomach in the region referred to in Fig. 1.

Gastroscopic examination, by Dr. Porter P. Vinson, of Richmond, Va., revealed "a polypoid mass on the lesser curvature of the stomach near the cardia, without evidence of ulceration. It was concluded that this lesion represented a localized area of polyposis."

On the basis of the roentgenologic and gastroscopic findings a tentative diagnosis, polypoid tumor of the stomach, was made and exploratory laparotomy was advised.

Operation.—The patient entered the University of Virginia Hospital April 18, 1940, and after four days of preoperative treatment, laparotomy was performed.

Spinal anesthesia was employed, and the abdomen was explored through an incision in the midline of the epigastrium. Exploration of the abdominal viscera revealed no abnormality, except in the case of the stomach. There were numerous large and tortuous vessels in the upper half of the stomach wall along the lesser curvature. In addition there was a good deal of telangiectasis of the surface vessels of the stomach in this region. To palpation the involved area of the stomach wall felt like

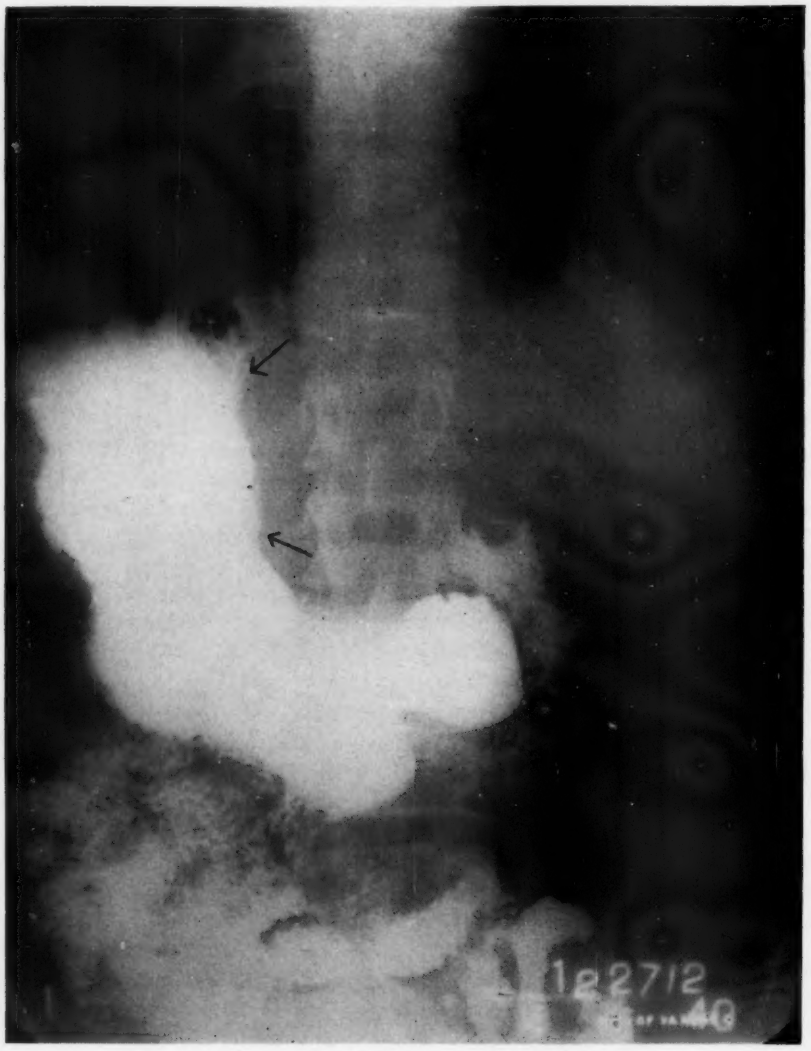


Fig. 1.—Case 1. Roentgenogram of stomach after barium meal, revealing ragged area on the lesser curvature beginning at the level of the cardiac orifice and extending downward for 6.5 cm.

a mass of angleworms. The changes were characteristic of the cavernous type of hemangioma. It was not sharply circumscribed and merged into normal looking stomach toward both the pylorus and greater curvature.

The involvement was so widespread that surgical eradication of it would have necessitated practically a total gastrectomy. This did not seem justified. A biopsy, however, seemed worth while. An incision was made high up in the stomach near the lesser curvature, and the stomach examined internally. As might have been expected,

bleeding was profuse but was readily controlled. Inspection confirmed the x-ray and gastroscopic findings in that the mucosa of the stomach, in the region referred to, was full of tortuous ridges and furrows representing the vessels beneath the surface. There was no evidence of polyposis or ulceration. A small area of the stomach wall on one side of the gastric incision was excised for later microscopic study, and the incision then closed. The appendix was removed routinely, and the laparotomy wound closed.

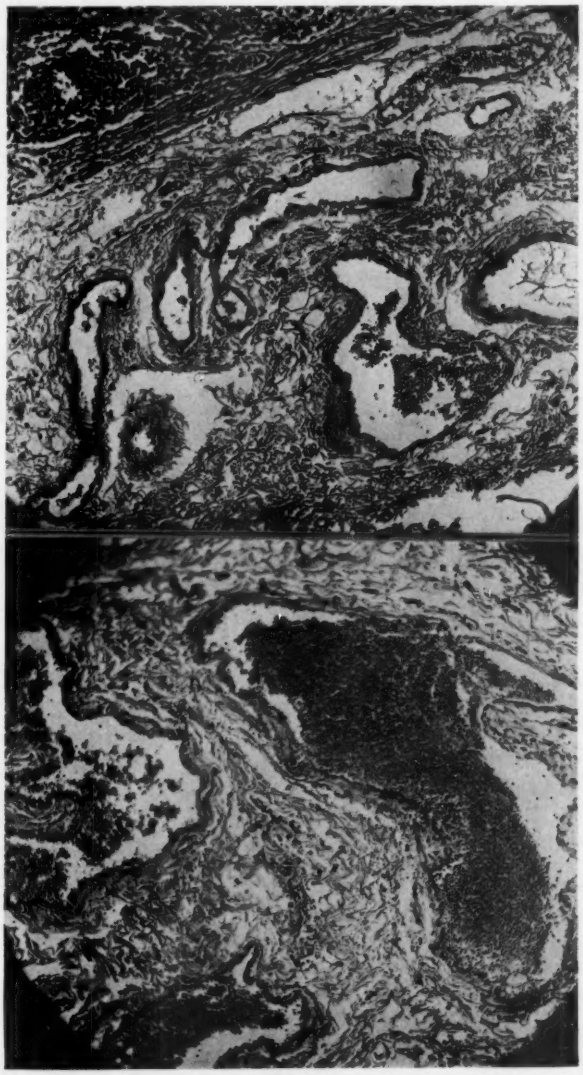


Fig. 2.—Case 1. *A*, Photomicrograph of submucosal area of stomach wall revealing many thin-walled blood vessels containing various amounts of blood. Mucosa and muscularis mucosae running obliquely across the top. (×25.) *B*, Higher power photomicrograph of submucosa revealing three thin-walled vessels in close proximity filled with blood (×60).

Microscopic Study.—Sections included the entire thickness of the stomach wall with a fairly thick and essentially normal mucosa. The muscularis mucosa appeared normal. The submucosa was fairly thick, and contained a large number of fairly large blood spaces with thin walls lined with endothelium. The muscularis and serosa appeared normal. The endothelial lined spaces in the submucosa seemed to

indicate the presence of a cavernous type of hemangioma. The final diagnosis was "cavernous hemangioma of the stomach."

Course.—The patient's convalescence was smooth and uneventful. He left the hospital on the twelfth postoperative day, tolerating a five-meal gastric diet comfortably. He has recently reported that he has no gastric symptoms, but continues to restrict his diet as directed. Should symptoms ever reappear, it is probable that radiotherapy should be considered.

CASE 2.—Unfortunately, nothing is known of the clinical features of this case except that the patient was a woman, aged 36 years, operated upon in a small hospital in a nearby town. Efforts to obtain further information have been unavailing.

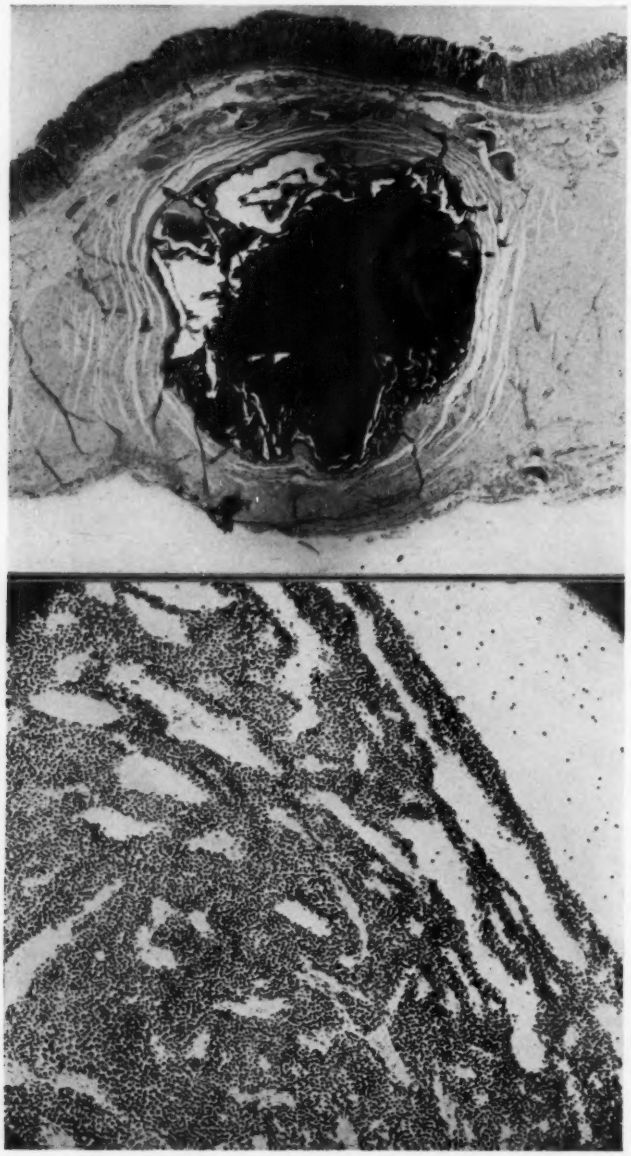


Fig. 3.—Case 2. *A*, Low-power photomicrograph revealing the small circumscribed angiomatous tumor entirely within the muscularis of the stomach wall (×10). *B*, Higher power photomicrograph revealing the mass of cells with very little stroma. The open blood spaces lined by endothelium can be seen. (×25.)

Tissue labeled "cyst of the stomach wall" was sent for study, and received by the Department of Pathology of the University of Virginia Hospital, Nov. 11, 1939. The tissue was in formalin fixative, and appeared to be relatively fresh. No other tissue accompanied the specimen, but it is impossible to know whether the tissue represented the patient's primary disease or was removed as an incidental finding during the course of an operation for some other disease.

Macroscopically, the tissue consisted of a small area of the entire thickness of the wall of the stomach, in the center a circumscribed mass 1 cm. in diameter, apparently representing a hemangioma in the muscularis.

Microscopically, the mucosa and submucosa were normal except for numerous dilated blood channels in the submucosa. Situated within the muscularis was an area which consisted of a mass of cells with very little stroma. The cells were rounded, fairly uniform in size and shape, and contained scanty cytoplasm with fairly large reticular nuclei. Situated within the mass of cells were numerous small and large channels which were lined by a flattened layer of endothelium, and were filled with blood. There was some invasion of the intermuscular spaces by the cells, but the lesion did not extend as far as the margins of the tissue removed. The final diagnosis was "cavernous and plexiform hemangioma of the stomach with rather marked endothelial proliferation."

SUMMARY

A brief review of hemangiomas and other benign tumors of the stomach has been given. Hemangiomas of the stomach appear to be quite rare. After a careful search of the literature, we have found only 12 previously recorded cases.

We have recorded two additional cases of hemangioma of the stomach discovered at operation. The first, a patient with a diffuse cavernous hemangioma involving a large area of the stomach wall and responsible for mild gastric symptoms, was studied gastroscopically. Though the tumor was not diagnosed correctly at the time of the gastroscopic examination, a definite organic lesion was noted. No previously recorded case of hemangioma of the stomach appears to have been examined gastroscopically. The second case report is incomplete and, because of our inability to obtain clinical data, is based only on the gross and microscopic study of tissue removed at operation elsewhere.

REFERENCES

1. Burty, M.: Un cas de volumineux, angio sarcome sous-muqueux, pédiculé de la grande courbure de l'estomac, Paris chir. **6**: 731, 1914.
2. Eiselsberg: Quoted by Moura, De Brito, and Lopes.[16]
3. Eliason, E. L., and Wright, V. W. M.: Benign Tumors of the Stomach, Surg., Gynec. & Obst. **41**: 461, 1925.
4. Eusterman, G. B., and Senty, E. G.: Benign Tumors of the Stomach, Surg., Gynec. & Obst. **34**: 5, 1922.
5. Geschickter, C. F.: Tumors of Blood Vessels, Am. J. Cancer **23**: 568, 1935.
6. Geschickter, C. F. Personal communication.
7. Guisez, M.: Angiome du cardia, diagnostique esophagoscopique, Larynx **6**: 201, 1913.
8. Hillstrom: Quoted by Rigler.[17]
9. Konjetzny, G. E. U., and Anschütz, W.: Die Geschwülste des Magens, Deutsche. Chir. **46**: 387, 1921.
10. Lammers, R.: Angioma ventriculi simplex, Inaug. Diss., Greifswald, Abel, 1893. (Cited by Lemon and Siebner.)

11. Lemon, W. S.: Angioma of the Stomach, Med. Rec. **97**: 220, 1920.
12. Lockwood, B. C.: Benign Tumors of the Stomach, J. A. M. A. **98**: 969, 1932.
13. Minnes, J. F., and Geschickter, C. F.: Benign Tumors of the Stomach, Am. J. Cancer **28**: 136, 1936.
14. Moore, A. B.: A Roentgenologic Study of Benign Tumors of the Stomach, Am. J. Roentgenol. **11**: 61, 1924.
15. Moore, A. B.: Benign Tumors of the Stomach From the Roentgenologic Point of View, J. A. M. A. **89**: 368, 1927.
16. Moura, P., De Brito, J. A., and Lopes, C. X.: Trois cas de tumerus benignes de l'estomac, J. de chir. **43**: 363, 1934.
17. Rigler, L. G.: Roentgenologic Observations on Benign Tumors of the Stomach, Am. J. Surg. **8**: 144, 1930.
18. Rigler, L. G., and Erickson, G. E.: Benign Tumors of the Stomach: Observation on Their Incidence and Malignant Degeneration, Radiology **26**: 6, 1936.
19. Schindler, R.: Gastroscopy, the Endoscopic Study of Gastric Pathology, Chicago, 1937, University of Chicago Press, p. 233.
20. Sherril, T. G., and Graves, F. S.: Hemangio-endothelio-blastoma of the Stomach, Surg., Gynec. & Obst. **20**: 443, 1915.
21. Siebner, M.: Hemangiom des Magens, Deutsche Ztschr. f. Chir. **241**: 176, 1933.
22. Stewart, M. J.: The Relation of Malignant Disease to Benign Tumours of the Intestinal Tract, Brit. M. J. **2**: 567, 1929.
23. Stockis, E.: Angiome de l'estomac chez un nouveau-né; mort par hémorragie, Ann. Soc. de méd. lég. de Belge **16**: 61, 1904-1905.

ABSCESS OF THE STOMACH WALL*

With Report of a Case

Paul K. Sauer, M.D., and James R. Lisa, M.D., New York, N. Y.

(From the Surgical Division and the Pathological Laboratory, City Hospital Welfare Island, Department of Hospitals, New York, N. Y.)

THIS communication is the report of acute abscesses of the wall of the stomach in chronic gastritis, occurring in the absence of chronic peptic ulcer. Abscesses of the stomach wall not directly the result of a demonstrable ulcer of the mucosal surface and not part of a phlegmonous

Fig. 1.—Mucosal surface of stomach with granular appearance and loss of rugae at pyloric end.

*Read before the New York Surgical Society, New York City, Nov. 9, 1940.
Received for publication, March 14, 1941.

gastritis must be considered a rare and unique phenomenon. Several pathologists among whom inquiries were made stated that they had never encountered it. A search of the literature failed to reveal a similar case.

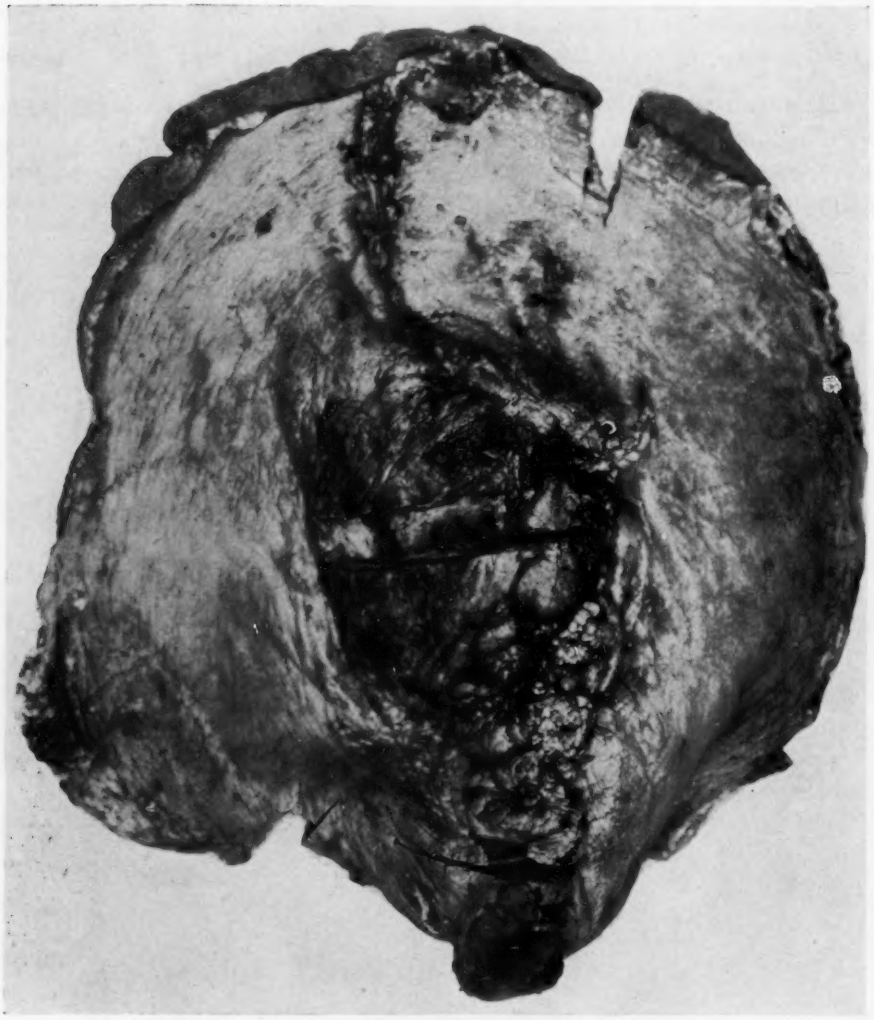


Fig. 2.—Serosal surface of stomach with abscesses.

CASE REPORT

The patient, a male, aged 35 years, a grocery clerk, was admitted to the Medical Service at City Hospital on Feb. 14, 1940, complaining of gaseous eructations and gnawing pains after eating, beginning two months previous to admission. The pain was increased by the ingestion of food and liquids. There was no nausea, vomiting, diarrhea, melena, or weight loss.

The general physical examination was entirely negative except for a tender spot in the epigastrium. The blood count showed 4,270,000 red cells and 90 per cent hemoglobin; W.B.C., 9,300; 62 per cent polymorphonuclears; and 38 per cent lymphocytes. The urine was essentially negative.

The roentgenogram showed the stomach to be orthotonic in type. Along the lesser curvature there was an indrawn area or niche formation which indicated infiltration. The duodenum was perfectly normal throughout. At six hours there was a very definite gastric retention lying along the greater curvature. There was a moderate gastric retention at twenty-four hours. The findings indicated ulceration of the prepyloric portion of the lesser curvature, possibly malignant.

A gastroscopy by Dr. H. Yarniss was reported as follows: "At the incisura in the region of the lesser curvature, posterior wall, there is a whitish ulcerated flat mass. Near the pylorus there are two whitish nodules. The action of the pylorus is asymmetrical, the lesser curvature behind the incisura not being visualized. From the gastroscopic picture there is an ulcerating carcinoma beginning at the incisura of the lesser curvature and also at the pylorus. *Diagnosis:* Carcinoma of the pyloric antrum involving the entire lesser curvature and pylorus."

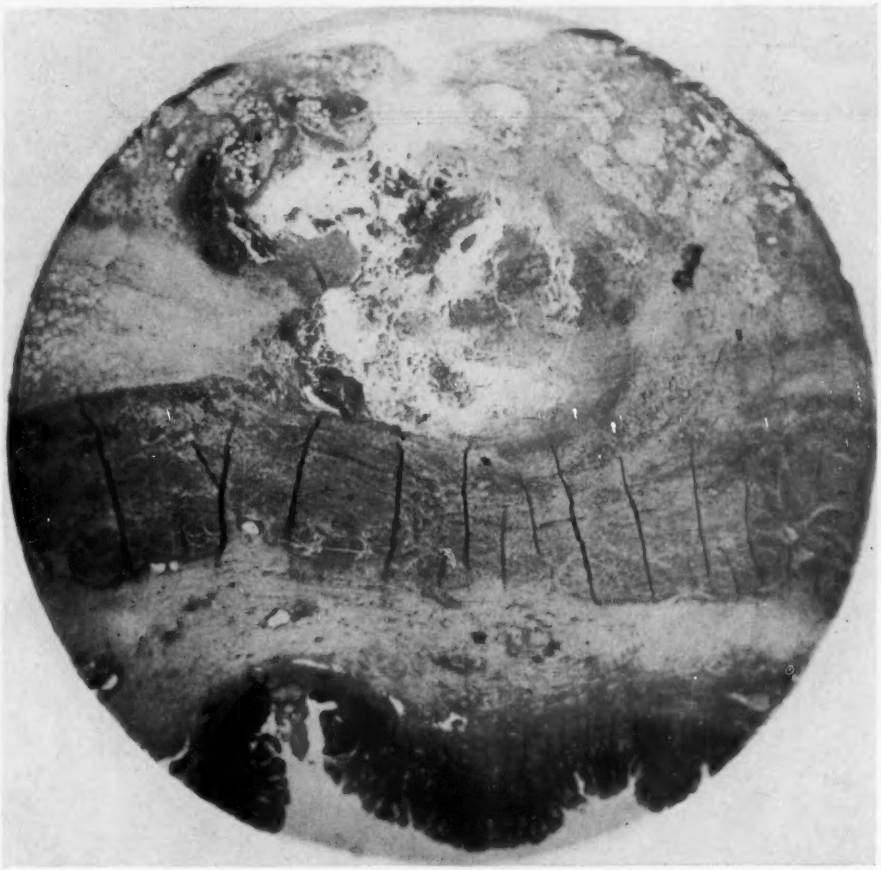


Fig. 3.—Abscess in section of stomach (low power).

On March 7 the patient was operated upon for what was thought to be an early carcinoma at the pylorus. On opening the peritoneum and examining the stomach and duodenum no evidence of carcinoma or ulcer could be found. There were no adhesions and the gall bladder was found to be normal. Further exploration, entailing an opening into the lesser omental cavity, revealed a firm mass about two inches in diameter on the posterior wall of the stomach near the lesser curvature at about the level of the reentrant angle. The character of the pathology, however, could not be definitely ascertained by either palpation or inspection. Based upon

the report of the roentgenologist and the gastroscopist it was decided that the lesion was probably an early carcinoma and a resection was indicated. Hence, a subtotal resection with a Hofmeister modification of a Polya anastomosis was done.

From an examination of the gross specimen after the operation, and even after consultation with the pathologist, the nature of the lesion could not be determined and had to be deferred until after examination of sections under the microscope.

Pathologic Report.—"The specimen consists of a partially resected stomach measuring 15 by 13 by 4 cm. The mucosal surface has lost its rugal markings in one half. This portion is granular in appearance and has two small areas near the pylorus somewhat redder than the surrounding portion and not definitely ulcerated. There is no evidence of depressions or scars of previous ulcers. The entire wall is greatly thickened and gelatinous in appearance. The serosa is markedly discolored and hemorrhagic. In the midportion of the serosa is a firm flat mass. Histologically, the entire wall is greatly thickened and diffusely infiltrated by lymphoid and plasma

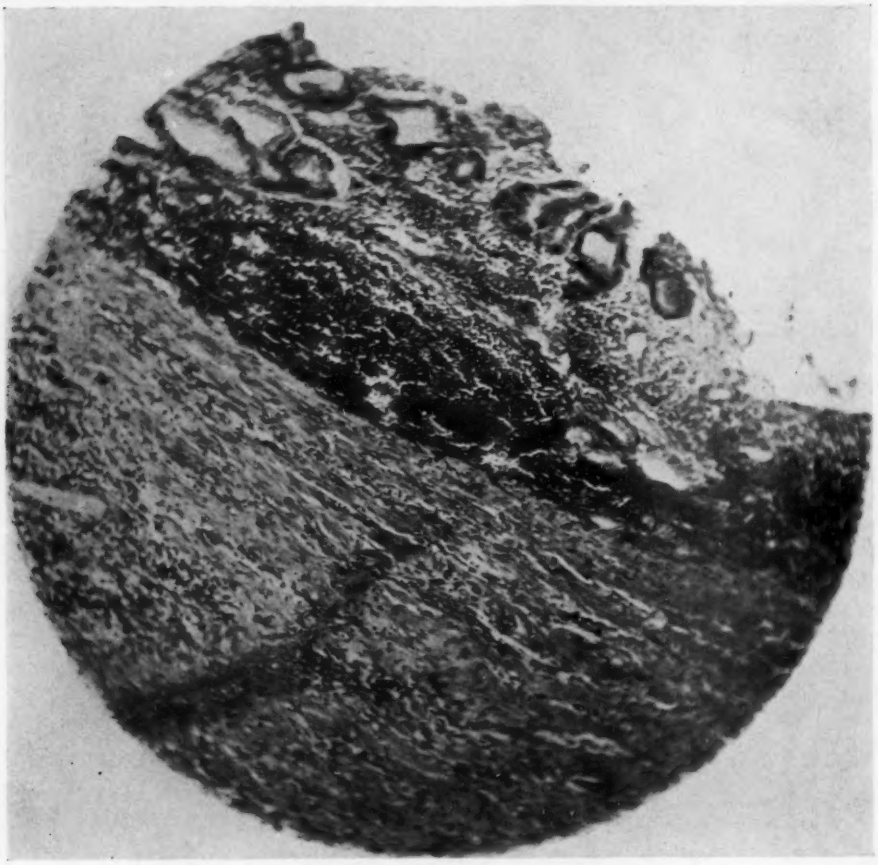


Fig. 4.—Abscesses in the subserosa (high power.)

cells. The architectural pattern of the wall is preserved and the epithelium intact except at the areas in the granular portion which, in the gross, appeared as small reddish areas. Shallow ulcers covered by a thin necrotic layer are present in this region. The surrounding portions are covered by a thin epithelium. The mass on the posterior surface consists of a group of numerous small subserous abscesses. No bacteria were demonstrated. *Diagnosis:* Chronic gastritis. Multiple acute subserous abscesses."

Although abscesses associated with phlegmonous gastritis are not uncommon, and abscesses in contiguity with gastric ulcers are occasionally seen, the character of the lesion just described seems to be unique. During the past ten years there had been only three cases of chronic gastritis at City Hospital which came to operation or autopsy. Two of these cases were seen on the operative service and one at autopsy. They differed, however, in their clinical history in that there was a characteristic history of ulcer of several months' duration in two instances, and in the third there was a history of ulcer for several years. Neither, however, showed subserous abscesses. The case found at autopsy presented a picture different from a chronic gastric ulcer, but an anemia very similar to a true pernicious anemia and nothing at all referable to the stomach. However, at autopsy there was a true phlegmonous gastritis.

The etiology of the abscess in this case is unknown. The findings, histologically, suggest that it is probably a true infectious lesion, most likely of low virulence since it caused so little disturbance in structural pattern and there is no large ulcer such as we see in other cases. Speculation might lead one to surmise that this is an early form of what later develops into a phlegmonous gastritis. If this be so, it is probably one of the earliest of this type of cases operated upon.

SUMMARY

1. A case of multiple subserous abscesses in a single locality of the stomach wall is described.

2. This case is considered unique as the literature is devoid of any report of a similar case.

3. The etiology remains obscure.

ZINC PEROXIDE IN THE TREATMENT OF COMPOUND FRACTURES AND TRAUMATIC AMPUTATIONS

A Report of 18 Cases

Edwin J. Pulaski, M.D.,* and B. H. Chandlee, M.D.,
Philadelphia, Pa.
(From the Frankford Hospital)

THERE is no unanimity of opinion about the treatment of compound fractures. Various techniques have been introduced and upheld by their proponents. However, the fundamental principles are the same. They are: (1) careful mechanical cleansing of the involved parts through débridement to remove all foreign material and devitalized tissue; (2) reduction of displacements and immobilization of the broken bones and adjacent joints and muscles; (3) administration of prophylactic antigas and antitetanus serums; (4) treatment of shock and excessive hemorrhage, if present.

Infection is one of the most important complications in traumatic wounds. All of these wounds are contaminated. In fact, in many wounds the contamination is so heavy that despite meticulous cleansing and the most gentle débridement, infection occurs. Furthermore, there are some types of contamination which the bodily defenses seem impotent to combat. A precise knowledge of the contaminating microorganisms present in the wound is essential. With this knowledge at hand, if hemolytic streptococci or *Staphylococcus aureus,* the gas gangrene bacilli, or other anaerobic bacteria are found, the surgeon is forewarned and, therefore, forearmed to take proper precautions against the development of infection.

This paper, first, will review some of the recent literature on the newer trends in the treatment of compound fractures; second, will present and analyze the results obtained following the use of zinc peroxide in such wounds; and third, will urge that all tissue débrided from traumatic open injuries be cultured aerobically and anaerobically.

Two methods of controlling infection in compound injuries are now receiving world-wide attention; viz., (1) the closed plaster treatment, and (2) use of the new chemotherapeutic agents. The former method consists of the immediate application of a plaster cast after the wound has been made mechanically clean by the removal of all foreign matter and by resection of all dead tissue that can be found. No antiseptic is applied. All treatment is then suspended for about a month. The proponents of this treatment claim that its success seems to depend less upon the virulence, number, and variety of bacteria present than

Received for publication, March 3, 1941.
*Presently at Presbyterian Hospital, New York City.

upon the powers of resistance of living tissue toward microbial infection. When the tissues are put at rest, lymphatic drainage is minimized, and secondary contamination is prevented. As recently pointed out by Higgs,[7] the method has its merits as well as its disadvantages. He states that the advantages are: (1) The relief of pain and toxemia; (2) immobilization of the limb and, at the same time, mobilization of the patient; (3) the promotion of highly vascular granulations owing to which (4) necrosis and sinus formation are exceptional and, (5) bony union takes place in a minimum of time. The disadvantages are: (1) The ever present danger of development of gangrene; (2) difficulty in maintaining reduction; (3) poor functional results, especially of fractures of the femur and humerus, which are said to be extremely poor; (4) the smell; (5) the wounds remain "messy" until the plaster is discarded (septic dermatitis is common); (6) the quality of the skin growing over the fracture is poor, often ridged and thickened, and frequently raw areas are present. Furthermore, other observers[23] state that suppuration may spread without visible inflammatory reaction, causing pyoarthritis at some distance away from the wound. Pressure sores may be produced. The closed plaster method, Trueta[31] states, cannot be used in the presence of cellulitis or already established anaerobic infection.

The sulfonamide group of drugs has been used orally and as a local antiseptic to prevent infection in compound fractures. Johnson[10] treated 36 cases of compound fractures with sulfanilamide orally, in addition to splinting, surgery, and prophylactic antiserums. Ten of the cases (27.7 per cent) had gross infection in the wounds, 5 with *Clostridium welchii,* 5 with hemolytic streptococci on smear or culture, others with staphylococci, *Bacillus coli,* and saprophytic organisms. Three cases developed gas gangrene, and amputation was necessary in one. All recovered. A fourth case developed a serious mixed bacterial infection and recovered. On the basis of these results the drug was believed "of curative value" and recommended as a valuable adjunct to treatment. However, lower incidence of infection in compound fractures has frequently been reported in the literature without the additional use of sulfanilamide. (Hermann,[6] 7 per cent in 398 cases; Poyner,[21] 6.3 per cent in 269 cases; Reynolds,[24] 19 per cent in 131 cases; Ritter,[25] 9 per cent in 100 cases.) As regards the local use of sulfanilamide as an antiseptic, Jensen, Johnsrud, and Nelson[8] described a series of 39 contaminated compound fractures in which the usual toilet of the wound was followed by the implantation of powdered sulfanilamide. All the wounds were then sutured, and all healed without infection except 2. These 2 did not become infected until the fractures were recompounded several days after being closed. In a control series of 94 cases similarly treated, except for the omission of sulfanilamide, 27 per cent of the cases were infected, including 7 cases of gas gangrene. No cultures of the wounds are reported, so that we do not know with

what organisms these authors had to deal. However, the difference between the treated and control group is striking. The report of Stuck and co-workers[30] would appear to confirm these results, although no control series is presented.

Key, Lembeck, and Burford[12, 14] confirmed the results of Jensen, Johnsrud, and Nelson, and they found that the presence of the drug in the fracture site did not interfere materially with the healing either of soft tissues or of bone. Key and his collaborators[13] state further that "powdered sulfanilamide in a wound is similar to a test tube experiment in which a concentration of the drug of approximately 1,000 mg. is brought in contact with any bacteria which may be present in the media. In such concentrations the drug is effective against small numbers of streptococci. However, if the number of staphylococci or Welch's bacilli is relatively large, infection may occur." Campbell[3] reported 54 cases of compound fractures wherein sulfanilamide was used both locally and systemically. He included cases where internal fixation also was employed. Infection developed in 10 cases (19 per cent). Cultures of these revealed *Staph. aureus* in 5, Welch's bacillus in 3, and *Str. hemolyticus* in 1. In one instance the infecting organism was not recorded. No control series was presented. Campbell states, "The evidence presented does not prove definitely that sulfanilamide either is or is not a preventive of infection in compound fracture." He believes, however, that the results are sufficiently encouraging to warrant further clinical trial for evaluation under controlled conditions.* Dunhill[4] and Mowlem[20] in referring to patients evacuated from Dunkirk believed that sulfanilamide orally in conjunction with the plaster method lessened the incidence of infection, although they admitted that reliable records were not obtainable at that time.

The sulfonamide group of drugs have not been shown to be specific against the gas gangrene organisms. The seven clinical case reports in the literature (Bohlman,[1] 3; Kennedy,[11] 1; Johnson,[10] 3) do not present convincing proof of the singular effectiveness of these drugs on gas gangrene. The experimental evidence is discouraging. Caldwell,[2] Henderson and Gorer,[5] Legroux,[15] Lockwood,[16] Morales-Otero and Gonzalez,[18] Singer,[27] Spray,[28] and Stephenson and Ross[29] were unsuccessful in protecting or saving experimental animals when intramuscular injections of pathogenic clostridia were given. The English authors found that a combination of sulfapyridine with specific antiserum gave some encouraging results.

Recently, however, we have had at our disposal another local antiseptic which, in conjunction with surgery, shows promise as a valuable aid in the prevention of infection. This antiseptic is zinc peroxide.

*A recent article by Campbell and Hughes (J. A. M. A. **117**: 672, 1941) gave somewhat more encouraging results, but they got 18.1 per cent infections still in 143 cases; the differences in percentage of infections between the "control" and "sulfanilamide treated" cases, while striking, are not significant on checking by the statistical method.

Johnson and Meleney[9] have shown that it not only has a continuous inhibiting effect on the hemolytic streptococcus, the gas gangrene organisms, and other anaerobic bacteria, but has as well bactericidal and detoxifying action. In 20 per cent concentration it also has bacteriostatic action against *Staph. aureus* and in clinical use the 40 per cent suspension has a favorable effect on staphylococcus in pure or in mixed infections in vivo. It has been shown to be noninjurious to tissues and noninhibitive to the healing processes. Furthermore it never manifests any general toxicity to the patient. Meleney's success with its use in chronic burrowing undermining ulcers has been confirmed.[25] The rapid disappearance of the Welch bacillus in clinical gas gangrene as reported by Meleney[18] seemed to demonstrate the efficacy of zinc peroxide in that condition. Wright[32] reported the use of zinc peroxide in osteomyelitis and compound fractures as an adjunct to the closed plaster method of treatment. After débridement he dressed the wounds with zinc peroxide combined in the proportion of 3½ ounces of zinc peroxide mixed with 4 ounces of cod-liver oil. The wounds were then enclosed in plaster and not dressed for four weeks. On redressing there presented a healthy granulating wound in the process of epithelization and free from odor. The wound was then redressed as necessary. Caldwell[2] was able to save 4 of 5 animals with experimentally produced *Cl. welchii* infected compound fractures by the use of zinc peroxide in the wounds following débridement and irrigation. In the same series of experiments the use of sulfanilamide crystals instead of zinc peroxide resulted in the survival of only 4 of 19 animals.

In compound fractures the incidence of infection is high. If the primary surgical procedure does not remove all the injured tissue, or is delayed, infection approaches 100 per cent. A recent study of the bacterial flora of 200 acute traumatic wounds confirmed the impression that all wounds are contaminated.[22] The bacteriologic methods are fully reported in the previous paper. The bacteria found were: *Staph. aureus*, 104 times (52 per cent); hemolytic streptococci, 34 times (17 per cent); nonhemolytic streptococci, 53 times (26.5 per cent); green streptococci, 18 times (9 per cent); clostridia, 46 times (23 per cent); enterobacilli, 46 times (23 per cent); and the anaerobic gram-negative bacilli, 3 times (1.5 per cent). Dirty wounds were apt to yield hemolytic streptococci and the gas gangrene producing anaerobic bacilli more frequently than "clean" wounds. On the basis of these findings it seemed logical to us that since zinc peroxide is effective in vivo and in vitro against most of these organisms, its use in compound fractures and traumatic amputations would be advantageous and would reduce the number of infections. This paper is a report on 18 compound fractures and amputations treated with zinc peroxide. There are presented, as a control, 23 consecutive compound fracture cases treated similarly, except that zinc peroxide was not used. All cases were street

or industrial accidents. All the cases reported herein were seen within 3 hours of the injury.

PROCEDURE

On arrival in emergency ward the wound was usually first covered with several layers of an alcohol dressing, and the injured limb was placed in a splint. Tetanus (1,500 units) and gas bacillus (3,500 units) antitoxins were given. If there was gross, excessive bleeding, the bleeding vessels were clamped. Shock therapy was instituted if indicated and immediate blood grouping for transfusion done. If the patient was in shock, he was given morphine, kept warm with blankets, and given an infusion of hypertonic saline solution and dextrose. He was not moved until the blood pressure, pulse, and respirations were favorable. X-rays were always taken before and after reduction.

Next, the patient was taken to the operating room and anesthetized. The skin surrounding the wound was shaved and cleansed. The injured soft tissue was then widely exposed, with enlargement of the skin wound as necessary, and carefully cleansed. Cultures were taken of the devitalized, débrided tissue. An attempt was made to remove all foreign bodies, and to eliminate blood clots and dead and devitalized tissue. All surfaces were carefully irrigated with copious quantities of saline solution. Soap and water were used to clean greasy and dirt-stained tissues (the use of ether for this purpose was abandoned because of the resultant damage to the tissues).

After thoroughly cleansing the wound, the fracture were reduced. The fragments were retained properly by internal fixation or by single wire traction on the extremity. The wound was then flooded with a freshly prepared suspension of active zinc peroxide in sterile distilled water, filling all of the nooks, crannies, and recesses of the wound. The wound was then covered with a thin layer of cotton soaked in the zinc peroxide suspension, this in turn covered with cotton soaked in water, and sealed with several layers of fine meshed gauze impregnated with vaseline or zinc oxide ointment.

Three things are essential for the successful use of zinc peroxide:

1. It must be an effective preparation (du Pont zinc peroxide distributed by Merck and by Mallinckrodt is satisfactory).
2. It should be brought into contact with every part of the wound as a creamy suspension (about 40 per cent in sterile water).
3. It should be kept wet. Water facilitates the continuous production of fresh hydrogen peroxide as the oxygen is liberated from the zinc peroxide.

Redressing daily or every second day was done, depending on the individual case. For the first few days the zinc peroxide was found adherent to the tissues. This was left alone. However, on irrigating the wound and removing the loose particles and whatever exudate was present, one was struck by the minimal inflammatory reaction and

absence of edema. The wound was then redressed as before. The zinc peroxide did not appear to prevent the formation of granulation tissue, for its presence became quite obvious after the third to the fifth day. It rapidly increased, and as this happened, the adherent zinc peroxide became free and was washed away. When the wound was filled with granulation tissue, it was ready for secondary closure or grafting.

The results with this method of treatment are presented in Table II.

TABLE I

CONTROL SERIES, 23 CASES COMPOUND FRACTURES (1938-1939)

NO. CASES	INJURY	DEATHS	INFECTIONS
4	Compound fractures of bones of skull; treatment consisted of debridement, elevation of bone fragments, and closure without drainage; cerebral concussion complicated 3 cases of the 4	0	0
2	Compound fractures of humerus, both in conjunction with compound fractures of skull and internal head injuries; one with simple fracture femur; both died, one 9 hours after arrival, the other 36 hours; the latter had infection in arm at time of death; treatment was for shock and débridement of wound; in the former there was not sufficient time for infection to develop	2	1 (50 per cent)
3	Compound fractures of radius and ulna; treatment: débridement, reduction and immobilization; one had associated multiple rib fractures, fractured pubis, and internal injuries; died 36 hours after arrival	1	0
3	Compound fractures metatarsals and phalanges; débridement and reduction and immobilization in 2; no infection; amputation of foot necessary in third; severe gas gangrene developed; *Staph. albus,* nonhemolytic streptococcus, *Cl. welchii* on culture; amputation through lower third of leg; given eighteen 20 c.c. doses antiserum, x-radiation, two blood transfusions, hydrogen peroxide, sulfanilamide; reinfection with gas gangrene; midthigh amputation necessary; recovery	0	1 (33 per cent)
11	Compound fracture of tibia and fibula; four had internal fixation after débridement and no infection; seven had single wire traction and suspension in Thomas splint or plaster gutter; one developed a *Staph. aureus* infection which cleared, and another a *Staph. aureus* osteomyelitis which required partial ostectomy with fair functional result; a third case developed a trivial local infection; no cultures were taken; one death, a 73-year-old white male from shock and myocardial failure	1	3 (27.2 per cent)
23 cases		4 deaths	5 infections or 21.8 per cent

TABLE II

EIGHTEEN PEROXIDE TREATED CASES (1939-1940)

NO.	INJURY	CULTURE DÉBRIDED TISSUE	TREATMENT	COMPLICATIONS	RESULT
		A. Ambulatory Cases			
2551	Traumatic amputation phalanges	*Staph. albus, B. proteus*	Débridement, splint, T.A.T., zinc peroxide cream dressings	None	Healed without infection
3561	Traumatic amputation phalanges	*Staph. albus, Staph. aureus, B. subtilis*	Débridement, splint, T.A.T., zinc peroxide cream dressings	None	Healed without infection
3810	Traumatic amputation phalanges	*Staph. albus,* hemolytic Streptococci microaerophilic	Débridement, splint, T.A.T., zinc peroxide cream dressings	None	Healed without infection
3874	Traumatic amputation phalanges	*Staph. albus, Staph. aureus,* hemolytic streptococci, *M. tetrag., B. cereus*	Débridement, splint, T.A.T., zinc peroxide cream dressings	None	Healed without infection
1877	Traumatic amputation phalanges	*Staph. albus,* nonhemolytic streptococci anaerobic	Débridement, splint, T.A.T., zinc peroxide cream dressings	None	Healed without infection
3732	Compound fracture phalanges	*Staph. albus,* nonhemolytic streptococci anaerobic	Débridement, reduction, splint, T.A.T., zinc peroxide cream dressings	None	Healed without infection
3885	Compound fracture dislocation phalanges	*Staph. albus, B. subtilis,* nonhemolytic streptococci	Débridement, reduction, primary closure, T.A.T., splint	Inflamed, serosanguineous exudate; reopened; no cult.; zinc peroxide cream dressings	Infection resolved rapidly with zinc peroxide cream therapy; wound healed
3727	Compound fracture phalanges	*Staph. albus, Staph. aureus,* hemolytic streptococci	Débridement, reduction, primary closure, splint, T.A.T.	Infection; reopened; culture, *Staph. aureus,* zinc peroxide cream dressings	Infection cleared with zinc peroxide cream therapy; wound healed

1099	Bullet wound dorsum hand; compound comminuted fracture proximal phalanx of thumb	*Staph. albus, Staph. aureus,* nonhemolytic streptococci anaerobic	Débridement, removal of bullet, T.A.T., and antigas serum, zinc peroxide cream dressings, splint	None	Healed without infection
			B. Hospitalized Cases		
4972	Compound fracture 2-3-4 metacarpals; avulsion skin fingers and hand	*Staph. albus, M. tetrag., Cl. tertium*	Débridement, T.A.T., antigas serum, zinc peroxide cream dressings	None	Successful skin graft; healed without infection
1811-H	Crushing injury foot; partial amputation	*Staph. albus,* hemolytic streptococci, *C. welchii*	Chopart amputation, skin flap prepared, T.A.T., antigas serum, zinc peroxide cream dressings	None; secondary closure skin flap	Healed without infection
1807-H	Traumatic amputation middle third humerus	*Staph. albus, B. subtilis,* hemolytic streptococci, *Cl. welchii*	Débridement, preparation of skin flap, T.A.T., antigas serum, zinc peroxide cream dressings	Death fourth day; myocardial failure	Stump not infected; swab culture immediately; P.M.: *Staph. albus*
2122-H	Traumatic amputation middle third arm by steel combs of wool-sorting machine; multiple puncture wounds above amputation site	*Staph. albus, B. anthracis,* hemolytic streptococci	Débridement, loose closure with rubber drainage, T.A.T., antigas serum, antianthrax serum, sulfanilamide, 16 Gm. in 4 days	Stump and lateral chest wall became puffy; gelatinous slough; wound reopened; zinc peroxide cream dressing; culture fifth day: hemolytic streptococci, *Staph. albus*	Wound granulating and healing; ninth day developed right heart failure, followed by hemolytic streptococcic pneumonia, then hemolytic streptococcic meningitis; 49 Gm. sulfanilamide and sulfapyridine given without effect; died twenty-fourth day; stump not infected

TABLE II—CONT'D

NO.	INJURY	CULTURE DÉBRIDED TISSUE	TREATMENT	COMPLICATIONS	RESULT
654-H	Compound fracture tibia and fibula; multiple lacerations, deep, of leg	No cultures taken	Débridement, T.A.T., antigas serum, single-wire traction, zinc peroxide cream dressings	Died fourth day; traumatic shock; myocardial failure	No infection at time of death
1434-H	Avulsion cheek; lacerated masseter muscle, upper lip and gum; comminuted fracture maxilla into sinus; deep lacerations of neck	No cultures taken	Débridement, shock therapy, T.A.T., antigas serum, boric acid compresses, 10 per cent mercurochrome into maxillary sinus	Wounds infected; culture: *Staph. albus,* hemolytic streptococci; zinc peroxide cream irrigation and dressings	Infection cleared; secondary closure and plastic surgery
3077-H	Lacerations lips, chin, and cheek with compound fracture maxilla into sinus; puncture wound through lower alveolar process	No cultures taken	Débridement, shock therapy, T.A.T., primary closure	Chin and cheek wounds infected; no cultures taken; zinc peroxide cream dressings and mouth irrigations	Suppuration ceased; zinc peroxide cream applied to alveolar process after extraction teeth upper maxillary; all wounds healed
1467	Extensive lacerations scalp with devitalization; fracture of right parietal bone	*Staph. albus, M. tetragenus,* hemolytic streptococci	Débridement, T.A.T., zinc peroxide cream; shock therapy	None	Granulated and healed without infection
1601	Multiple lacerations and gunpowder burns, head and face; compound fracture right parietal bone	*Staph. albus, Staph. citreus,* nonhemolytic streptococci	Débridement, elevation of depressed fragment, zinc peroxide cream dressings	None	Wounds healed without infection

RESULTS

The control series of 23 consecutive compound fractures admitted to the hospital during 1938-39 are presented in Table I. This series is comparable to the inpatient cases in the zinc peroxide group. The outpatient record of the non zinc peroxide-treated compound fractures does not permit a comparison with the zinc peroxide cases treated as outpatients. In 16 cases of the control series no infection developed. In 2 other cases 1 patient died 9 hours and the second 36 hours after admission, and there was no clinical evidence of infection. Five cases (21.8 per cent) developed infection. In 7 cases the wounds were closed. Infection (gas gangrene) developed in 1 of these (14.2 per cent). In 16 cases the wounds were left open. Infection developed in 4 (25 per cent). In 1 the stump of an amputated arm appeared infected at the time of death, the second day after injury. The second was a mixed infection due to *Staph. aureus* and hemolytic streptococci. The third was a trivial infection from which no cultures were taken. The last case developed a *Staph. aureus* osteomyelitis. The differences in percentage of infections between the closed and open wounds is partly explained by the fact that only the most favorable cases, as regards degree of contamination and devitalization of tissue, were closed. The more serious and dirty wounds were left open. Four of the patients in this series died. There were no deaths attributed to infection.

The treated series covers a period of one year, beginning July, 1939, during which 18 cases of compound fractures received zinc peroxide locally in addition to surgery, splinting, and administration of tetanus and gas bacillus antisera. There were 10 injuries to the phalanges, 1 crushing injury of the foot, 1 fracture of the tibia and fibula, 2 traumatic amputations of the humerus, and 4 fractures of bones of the skull. In 13 patients the wounds were left open and treated with zinc peroxide, and no infections developed. From 5 of these hemolytic streptococci were cultured from the débrided tissue fragments, from 3, nonhemolytic anaerobic streptococci, and from 2, *Cl. welchii.* Staphylococci were present in conjunction with these organisms in every case. In 1 patient the wound was left open and treated with 10 per cent mercurochrome and boric acid compresses. Infection developed yielding hemolytic streptococci but cleared rapidly with the change to zinc peroxide applications. In 4 patients the wounds were closed following débridement and reduction, and each wound subsequently became infected. Two yielded hemolytic streptococci on preliminary culture; 1 also had an aerobic nonhemolytic streptococcus, and another, *B. anthracis.* In the fourth case no cultures were taken. After opening the wounds and treating them with zinc peroxide, the infections promptly cleared. There were 3 deaths in this series. Two were in men over 70 years of age and were attributed to uncontrollably severe

shock and myocardial failure. The third death was twenty-four days after the accident and was due to a hemolytic streptococcus, cerebrospinal meningitis, and pneumonia. Sulfanilamide and sulfapyridine were not effective. The wounds in all 3 patients were benign and healing at the time of death.

COMMENT

Zinc peroxide dressings bring about a prompt visible change in the appearance of the wounds treated. For the first two days the surface of the wound is gray with adherent particles of the zinc peroxide. One is struck by the absence of any swelling, redness, or other indication of inflammation. On the third or fourth day pinpoint granulations appear and rapidly spread over the entire wound surface. The new tissue is bright, shiny, red, and firm, and there is no evidence of the invasion or activity of micro-organisms. The change of dressings every day or every other day does not disturb the immobilization of the fracture. The dressing probably could be left much longer without changing. Meleney[17] has left zinc peroxide dressings as long as nine days in the perineal wound of an abdominoperineal operation. Wright[29] has left them sealed under plaster in compound fractures for four weeks.

Zinc peroxide does not interfere with the radiographic evidence of callus formation. Although it is radiopaque, it can be easily distinguished. It does not get lost in the interstices of the wound but is discharged by the proliferation of granulation tissue. Because it is not absorbed, it should not, of course, be used in wounds which are to be closed. In open wounds, however, with the use of zinc peroxide, serious infections with gas gangrene organisms, and other anaerobic bacteria, as well as with hemolytic streptococci and other susceptible organisms, are avoidable. Infections due to susceptible organisms respond rapidly when the drug is brought in apposition to the infected tissue. Zinc peroxide never manifests any general toxicity to the patient. Its use in compound fractures obviates the objectionable odors attendant upon the closed plaster method. While the series is small because of the termination of resident service, the results obtained are sufficiently encouraging to warrant further use of zinc peroxide prophylactically in the prevention of infection in compound fractures.

SUMMARY

1. The recent literature on compound fracture therapy is reviewed.

2. Traumatic wounds are always contaminated. The most virulent contaminating organisms are the hemolytic streptococci, the clostridia, and other anaerobic organisms, all of which are susceptible both in test tube and in vivo to zinc peroxide.

3. The results on 18 cases of compound fractures and traumatic amputations treated with zinc peroxide are analyzed. Thirteen wounds left open and treated with zinc peroxide healed without infection. One

wound left open and treated with 10 per cent mercurochrome and boric acid became infected. Infection promptly cleared with zinc peroxide. Four wounds closed primarily became infected; on reopening, zinc peroxide therapy rapidly cleared the infections in each case. In 23 "control" cases not receiving zinc peroxide treatment, the incidence of infection was 21.8 per cent.

4. The method of using zinc peroxide in these cases is given in detail.

5. Finally, a plea is made for the routine aerobic and anaerobic culture of all traumatic wounds. Precise knowledge of the bacterial flora contaminating such wounds is essential, not only for the anticipation of and the prevention of infection, but also for the proper evaluation of the results of treatment instituted to combat it.

REFERENCES

1. Bohlman, H. R.: Gas Gangrene Treated With Sulfanilamide, J. A. M. A. **109**: 255, 1937.
2. Caldwell, G.: Treatment of Gas Gangrene Experimentally Produced, J. Bone & Joint Surg. **23**: 81, 1941.
3. Campbell, W. C.: Sulfanilamide and Internal Fixation in the Treatment of Compound Fractures, J. Bone & Joint Surg. **22**: 959, 1940.
4. Dunhill, Sir Thomas: Chemotherapy for War Wounds, Brit. M. J. **1**: 642, 1940.
5. Henderson, D. W., and Gorer, P. A.: Treatment of Certain Experimental Anaerobic Infections With Sulfapyridine and With Immune Sera, and Problem of Synergistic Action, J. Hyg. **40**: 345, 1940.
6. Hermann, O.: Compound Fracture Therapy at the Boston City Hospital, Arch. Surg. **40**: 853, 1940.
7. Higgs, S. L.: Closed Plaster Treatment of Wounds, Brit. M. J. **1**: 800, 1940.
8. Jensen, N. K., Johnsrud, L. W., and Nelson, M. C.: The Local Implantation of Sulfanilamide in Compound Fractures, SURGERY **6**: 1, 1939.
9. Johnson, B. A., and Meleney, F. L.: The Antiseptic and Detoxifying Action of Zinc Peroxide on Certain Surgical Aerobic, Anaerobic, and Micro-Aerophilic Bacteria, Ann. Surg. **109**: 881, 1939.
10. Johnson, R.: Chemotherapy in the Prevention of Infection in Compound Fractures, Am. J. Surg. **49**: 195-200, 1940.
11. Kennedy, W. C.: Therapy of Gas Gangrene With Report of Case; Illinois M. J. **73**: 260, 1938.
12. Key, J. A., and Burford, T. H.: Local Implantation of Sulfanilamide in Compound Fractures: Its Effect on Healing, South. M. J. **33**: 449, 1940.
13. Key, J. A., Frankel, C. J., and Burford, T.: The Local Use of Sulfanilamide in Various Tissues, J. Bone & Joint Surg. **22**: 952, 1940.
14. Key, J. A., and Lembeck, J. A.: Local Use of Sulfanilamide in Compound Fractures and Other Wounds, Indust. Med. **9**: 493, 1940.
15. Legroux, R.: Chemical Prevention of Bacterial Infection in War Wounds, Méd. Acad. de chir. **66**: 415, 1940.
16. Lockwood, J. S.: Sulfanilamide in Surgical Infections, J. A. M. A. **115**: 1190, 1940.
17. Meleney, F. L.: Personal Communication.
18. Idem: Zinc Peroxide in Surgical Infections, S. Clin. North America **1**: 707-708, 1936.
19. Morales-Otero, P., and Gonzalez, L. M.: Effect of Azosulfamide (Neoprontosil) in Experimental Welchii Infections in Mice, Proc. Soc. Exper. Biol. & Med. **44**: 532, 1940.
20. Mowlem, R.: Closed Plaster Treatment of Wounds, Brit. M. J. **1**: 801, 1940.
21. Poyner, H.: End Results in 1000 Consecutive Industrial Fractures, Texas State J. Med. **34**: 284-288, 1938.
22. Pulaski, E. J., Meleney, F. L., and Spaeth, Wm. L. C.: Bacterial Flora of Acute Traumatic Wounds, Surg., Gynec., & Obst. **72**: 982-988, 1941.
23. Ricard, Francillon, Deplante, and Mathevon: Treatment of Extensive Wounds of the Limbs by Plaster and Infrequent Dressings, Lyon chir. **36**: 573-583, 1939-40.

24. Reynolds, J. T., Zeiss, C. R., and Cubbins, W. R.: Compound Fractures, Arch. Surg. **40**: 844, 1940.
25. Ritter, H. H.: Management of Compound Fractures, Arch. Surg. **34**: 527-53, 1937.
26. Shallow, T. A., Fry, K. E., and Pulaski, E. J.: The Effect of Zinc Peroxide Treatment on Ulcers Due to the Micro-Aerophilic Hemolytic Streptococcus, Surg., Gynec. & Obst. **70**: 987, 1940.
27. Singer, E.: Experimental Studies on Combined Sulfanilamide and Serum Treatment of Gas Gangrene Infections, M. J. Australia **2**: 275, 1940.
28. Spray, R. S.: Bacteriostatic Action of Prontosil Soluble, Sulfanilamide and Disulfanilamide on the Sporulating Anaerobes Commonly Causally Associated With Gas Gangrene, J. Lab. & Clin. Med. **23**: 609, 1938.
29. Stephenson, D., and Ross, H. E.: The Chemotherapy of *Cl. welchii* Type A and *Cl. septique* Infections in Mice, Brit. M. J. **1**: 471, 1940.
30. Stuck, G., Maxwell, E. A., and Monsalvo, R. N. O.: Crystalline Sulfanilamides in Compound Fractures, Texas State J. Med. **36**: 225-228, 1940.
31. Trueta, J.: Treatment of War Wounds and Fractures, New York, 1940, Paul B. Hoeber, Inc.
32. Wright, P. B.: Osteomyelitis and Compound Fractures; Treatment With Zinc Peroxide and Codliver Oil, J. M. A. Georgia **28**: 59, 1939.

TREATMENT OF FRACTURES IN THE NECK OF THE HUMERUS WITHOUT IMMOBILIZATION

EDWIN O. GECKELER, M.D., PHILADELPHIA, PA.

(From the Fracture Service, Hahnemann Medical College and Hospital)

FRACTURE in the upper end of the humerus is a common occurrence in persons of advanced years, and until recently the permanent handicap which followed this injury was almost a foregone conclusion. Most of these fractures unite within a few weeks under any form of treatment, but with former methods as attention was directed to the fracture alone the end result in many instances was a poorly functioning limb. The disability not only was caused by adhesions and contractures which occurred in the shoulder joint from binding the arm to the chest, but also was due to prolonged immobilization of the other joints in the dressing.

In order completely to reduce and immobilize such a fracture, and to prevent much disabling tightness of the shoulder, we formerly used plaster of Paris spicas or body casts, which held the lower fragment of the humerus in the abducted position to meet the upper fragment. Fractures without displacement also were immobilized in partial abduction, in order to prevent the disability which resulted from binding the arm to the chest. However, although these body casts maintained complete reduction and prevented the disabling contracture of the shoulder caused by the Velpeau dressing, their heavy weight and awkwardness were a great burden to these older patients. Furthermore, such complete immobilization of the entire limb in plaster of Paris left the patients with the same muscular weakness and stiffness of joints which bandaging the limb to the body had produced. Our dissatisfaction with results prompted us to treat this injury in an entirely different manner.

RECENT DEVELOPMENTS

Watson-Jones[1] has simplified the treatment of fractures in this location by disregarding the customary classification of the anatomical and surgical necks of the humerus, dividing them into the abduction and adduction forms. The essential feature of reduction in most instances is moving the distal or shaft fragment to meet the proximal or immovable fragment, by adduction or abduction according to the displacement. The fragments will remain in a relatively normal position after reduction, providing the arm hangs at the side of the body, without support to the elbow. The hanging position for fractures in the neck of the humerus is rational. In discussing fractures above the insertion of the pectoralis major, Griswold[2] calls attention to the squeezing effect on the fragments

Received for publication, March 8, 1941.

by longitudinal muscles while traction is made with the arm held parallel to the body. Howard and Eloesser[3] have shown that tension of the tendon of the long head of the biceps controls the upper fragment by its pressure in the bicipital groove while the arm hangs by the side of the body, and the weight of the arm itself causes slight traction. Much less traction is needed in the adducted position than while the arm is held in abduction. Occasionally, in fractures high in the neck with marked adduction angulation, reduction can be obtained and maintained only by wide abduction. Obviously, in these cases the hanging position is contraindicated.

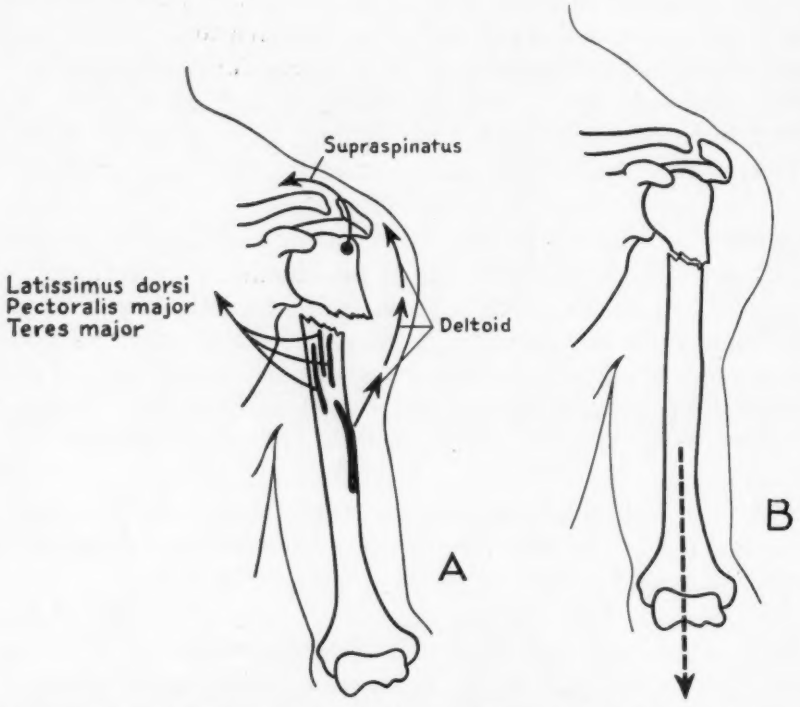
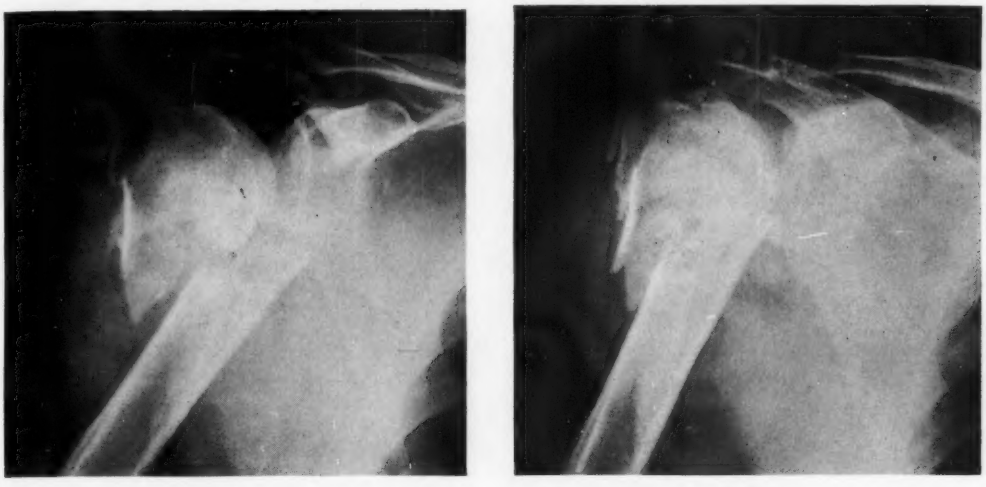


Fig. 1.—*A*. Typical fracture in the neck of the humerus, showing effect of muscular attachments in displacement of the fragments. *B*. Satisfactory alinement produced by the traction effect of the weight of the arm in the hanging position.

PERSONAL EXPERIENCES

For several years I examined fractures in the neck of the humerus under the fluoroscope to determine definitely which cases were impacted. The routine treatment for impacted fractures was rest in a sling for two weeks, after which activity was encouraged; in a number of instances the patients were observed to have commenced exercises of their own accord, as they had very little pain. Later the simple form of hanging cast for ambulatory traction as originally advocated by Caldwell[4] and subsequently recommended by Griswold and others was used. Caldwell's method[5] is a departure from the usual routine of complete and continuous immobilization, and consists of a heavy plaster of Paris cast applied

to the arm and forearm with the elbow held at a right angle; a loop of bandage is fastened to the plaster at the wrist, and this bandage is passed around the neck to form a sling. While wearing this the patient performs relaxed swinging exercises frequently, these exercises beginning the day after injury. This method was found to be a decided improvement. The atrophy caused by complete immobilization was prevented, and early exercises prevented limitation of abduction and rotational movements at the shoulder. A number of impacted fractures then were treated by early exercises alone, with excellent results.

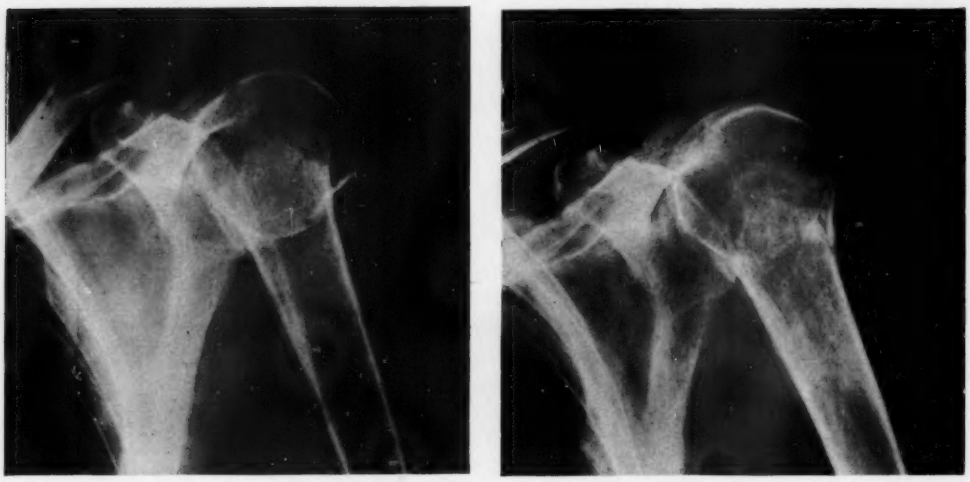


A. *B.*

Fig. 2.—*A*. H. M. Severe fracture before treatment. Note the rotation of the head, and extreme displacement of the shaft of the humerus. *B*. Same fracture as shown in *A*, after application of a simple sling from the neck to the wrist. The alinement of the fragments, although not perfect, was satisfactory and union with good function was secured by relaxed movements without immobilization.

Fig. 3.—Relaxed abduction and circumduction exercises of patient whose x-ray films are shown in Fig. 2. This photograph was made on the third day after injury. Note accompanying injury to the soft structures.

The favorable experience with impacted fractures treated by immediate voluntary motions, without immobilization or even a hanging cast, led to treating the unimpacted fractures in the same manner. This treatment was prompted by the observation that the fragments in unimpacted cases were held relatively immobile by muscle spasm, and that early relaxed movements by the patient as in stooping did not disturb the fragments or cause pain. There were numerous cases in which considerable movement of the fragments was noted under the fluoroscope, yet even in these instances a wide range of shoulder motions was obtained within a short time because the arm was treated without the customary immobilization. Later several extreme cases in which the fragments were markedly displaced were manipulated, and after reduction were treated in like manner. It was observed that cases of fractures caused by such indirect violence as falling on the outstretched hand recovered in a relatively shorter time, although comminuted fractures which were caused by direct force as falling on the side of the shoulder usually were followed by a longer period of disability on account of greater soft tissue injury. All of the fractures united within eight weeks.



A. *B.*

Fig. 4 *A* and *B*.—J. C., aged 68 years. Typical case, the fragments being moderately impacted but movable. Complete restoration of function after ten weeks. X-ray film five weeks after injury shows union.

These results demonstrated that easy, relaxed movements prevent muscular atrophy and limitation of shoulder function, and at the same time do not interfere with union. The patient will not move the limb further than to the point of discomfort, which range increases day by day, and thus there is no liability to displace the fragments. Absolutely no passive movements are given, as manipulation would interfere with union. In the upright position the arm cannot be raised forward or outward voluntarily, but, in stooping, the arm can be swung by relaxed

movements at the shoulder joint. Use of the hand and elbow for light occupations about the home is encouraged. The psychological element of this treatment also is helpful, as relaxed voluntary movements overcome the fear and consequent delay in recovery which are common after

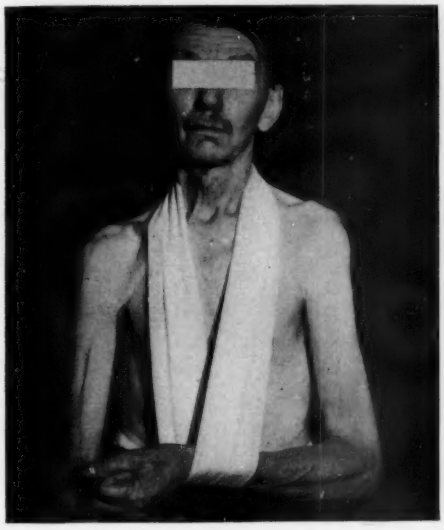


Fig. 5.

Fig. 6.

Fig. 5.—Simple sling from the neck to the wrist used for these fractures. The fragments are controlled by the traction from the weight of the arm, and by muscle tension. Note that the elbow is held at a right angle, and that this sling produces slight abduction at the shoulder.

Fig. 6.—Double exposure. Flexion and extension at the shoulder secured by the "sawing" exercise.

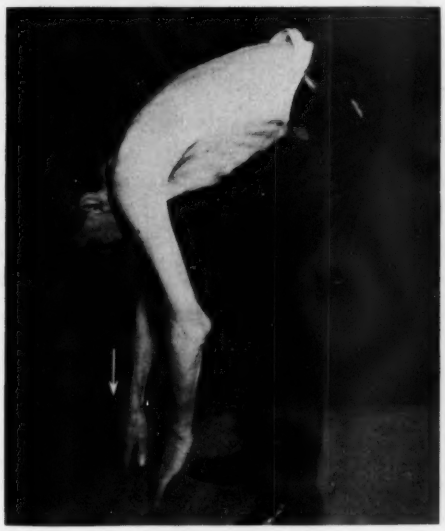


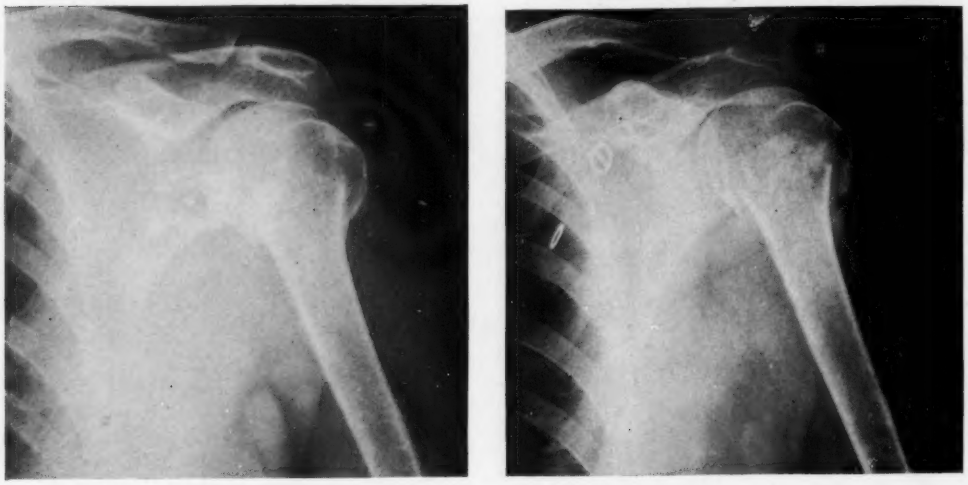
Fig. 7.

Fig. 8.

Fig. 7.—"Dipping" exercise, with the shoulder relaxed in stooping.

Fig. 8.—Circumduction by swinging movements, with the arm hanging in abduction. The patient must bend forward as far as shown. These relaxed movements are performed completely by the average patient within six weeks after injury. In the case shown there was 90 per cent of the normal range of voluntary movements after nine weeks.

any form of immobilization. In all of the instances there is a progressive return of shoulder motions, and union occurs as rapidly as in those treated by complete immobilization. Even in severe cases the sling from the wrist to the neck can be discarded after three or four weeks. Obviously a good result depends upon the complete cooperation of the



A. *B.*

Fig. 9 *A* and *B*.—L. G., aged 64 years. Fracture without impaction. Within six weeks after injury there was a free range of the relaxed movements and firm union.

Fig. 10. Fig. 11.

Figs. 10 and 11.—Functional result twelve weeks after fracture shown in Fig. 9. There is a complete range of abduction and of external rotation.

patient in following out the prescribed exercises thoroughly and often, and repeated instructions and check-up by the attending physician are necessary. In all of the fifteen cases I treated and under my supervision

Fig. 12. Fig. 13. Fig. 14.

Fig. 12.—M. H., 50 years of age. Good range of relaxed movements at end of six weeks; 75 per cent of normal strength and movements at end of twelve weeks.

Fig. 13.—C. M., 86 years of age. Satisfactory range of relaxed movements in six weeks; 75 per cent of normal range at end of eight weeks; 90 per cent of normal after five months.

Fig. 14.—B. C., 69 years of age. Excellent cooperation and relaxed movements. Result at five weeks was 50 per cent of normal function. No further follow-up.

Fig. 15. Fig. 16. Fig. 17.

Fig. 15.—L. K., 72 years of age. Probably impacted. Free from pain with voluntary abduction to 90 degrees in three weeks; 75 per cent of normal strength and motion after six weeks. No further follow-up.

Fig. 16.—A. F., 60 years of age. Voluntary movements 50 per cent of normal six weeks after injury; 90 per cent of normal at end of fifteen weeks.

Fig. 17.—H. M., 54 years of age. Seventy-five per cent of normal range of movements and returned to work as night watchman four weeks after injury.

Fig. 18. Fig. 19. Fig. 20.

Fig. 18.—S. T., 63 years of age. Ninety per cent of normal range of movements at end of eight weeks. Colles' fracture in same limb.

Fig. 19.—S. T., 80 years of age. Good cooperation in relaxed exercises; 75 per cent of normal range of movements by tenth week.

Fig. 20.—B. Y., 70 years of age. Average range of relaxed movements by end of six weeks. Continued improvement, with 66 per cent of normal function on last visit at ninth week.

the functional results were good. In three cases even without complete reduction the function was satisfactory on account of the preservation of movements.

SUMMARY

A simple and effective treatment for a majority of fractures in the neck of the humerus has been described. Its chief feature is the preservation of movements in the limb, in contrast to the former customary immobilization which often was followed by permanent limitation of movements and weakness. This method consists of supporting the wrist with a sling and encouraging immediate relaxed exercises. It is an exception to the general rule that all fractures must be immobilized for at least a preliminary period. Careful observation shows that the method described does not cause delay in union. It is recommended for all fractures in the neck of the humerus, except when fracture-dislocation or decided displacement exists.

REFERENCES

1. Watson-Jones, R. W.: Fractures and Other Bone and Joint Injuries, Baltimore, 1940, Williams and Wilkins Co.
2. Griswold, R. A., Goldberg, H., and Robertson, J.: Fractures of the Humerus, Am. J. Surg. **43**: 31, 1939.
3. Howard, N. J., and Eloesser, L.: Fractures of the Upper End of the Humerus, J. Bone & Joint Surg. **16**: 1, 1934.
4. Caldwell, J. A.: Unimpacted Fractures of the Surgical Neck of the Humerus, Am. J. Surg. **31**: 141, 1936.
5. Caldwell, J. A.: Fractures in the Shaft of the Humerus, Surg., Gynec. & Obst. **70**: 421, 1940.

TIBIAL EPIPHYSIOTOMY FOR SEVERE GENU RECURVATUM

ROSS SUTHERLAND, M.D., LOS ANGELES, CALIF., AND
M. JOHN ROWE, JR., M.D., LONG BEACH, CALIF.
(From the Tichenor Orthopedic Clinic, Long Beach)

THE correction of severe paralytic genu recurvatum is a major problem. Many surgical methods advocated have consisted of soft tissue corrective work which eventually has often allowed regression to the original deformity by action of the original causative factors.

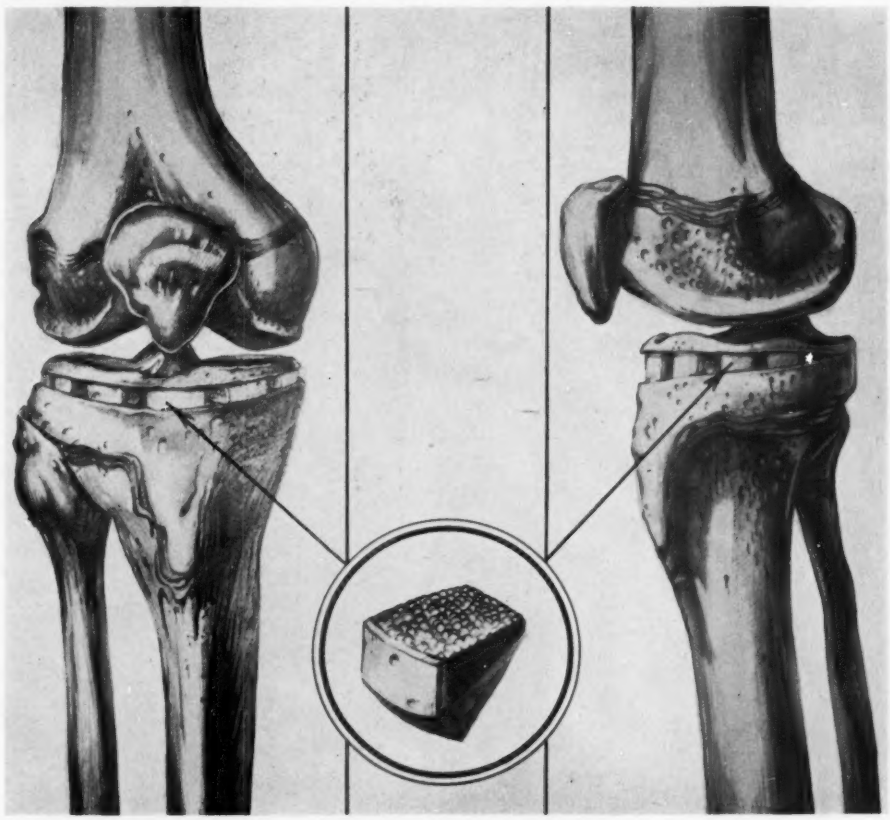
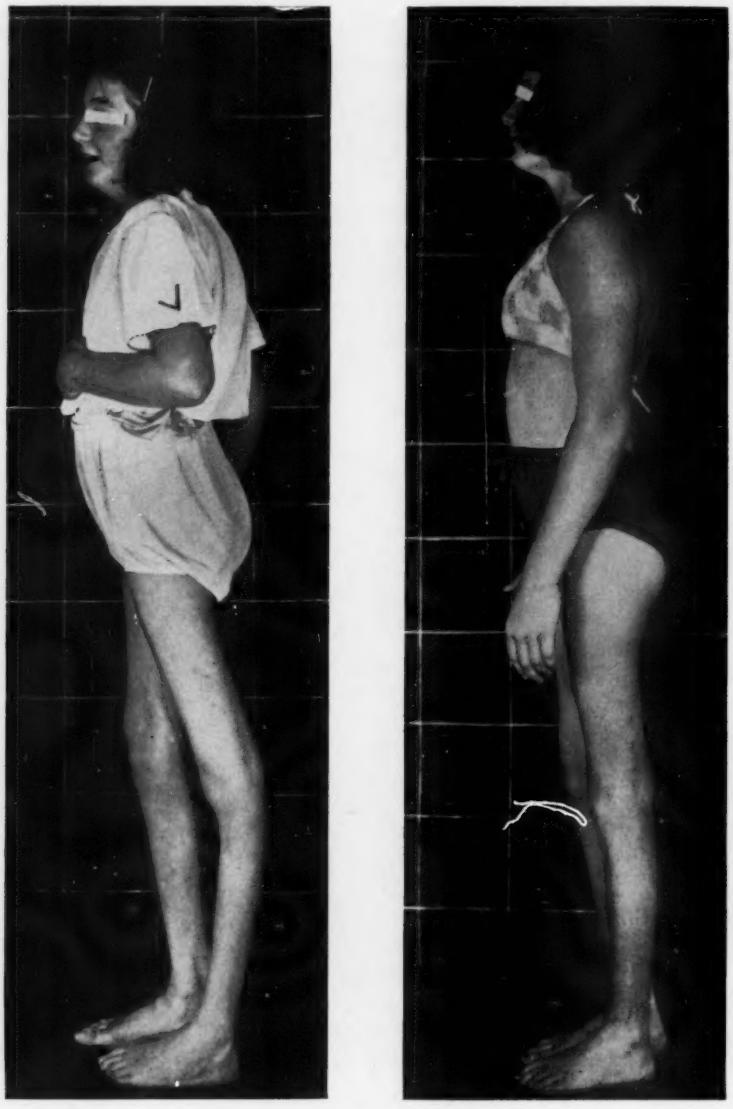


Fig. 1.—Tibial epiphysiotomy with wedge grafts from tibial crest.

The procedure here presented arose from observation of the necessity of splinting fractured tibial spines in complete knee extension to prevent flexion deformity. Recent work[1] has confirmed the belief that the tibial spines and anterior articular surfaces are the only bone block to extension of the knee, the other limiting factors being soft tissue (capsule, lateral and cruciate ligaments) and muscle action. Brett[2] has described a method of correction by elevation of the anterior articular surfaces

Received for publication, Aug. 6, 1941.

of the tibia in the mature adult after closure of the epiphyses. A comprehensive report[3] has demonstrated that all growth in length of the long bones occurs on the diaphyseal side of the epiphyseal line and that articular cartilage growth is at the articular surface.



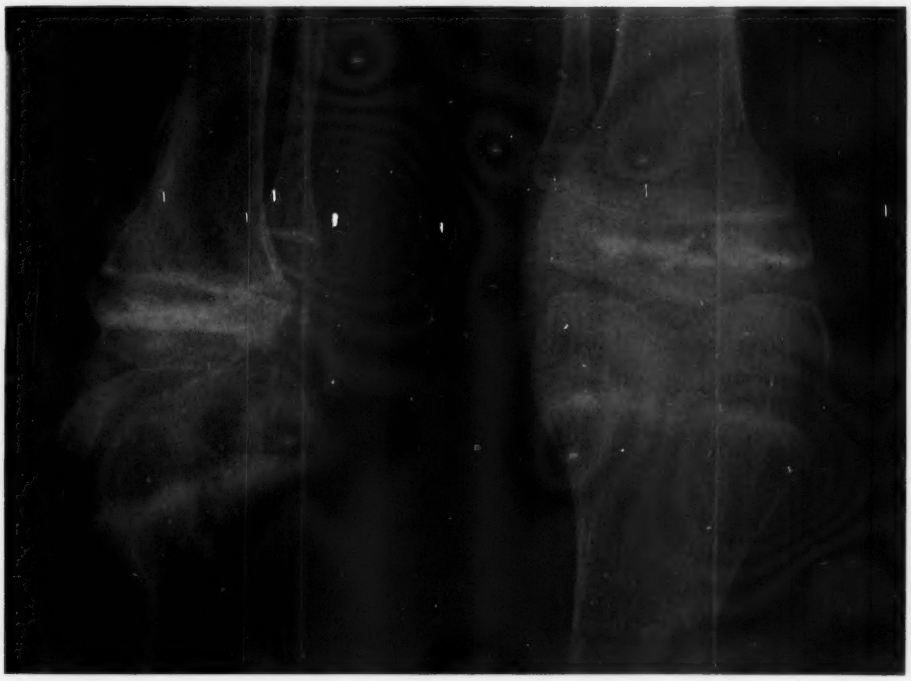
A. *B.*

Fig. 2.—Paralytic genu recurvatum. *A.* Prior to operation. *B.* Twelve weeks postoperatively.

Since experience has shown that corrective surgical procedures should make use of all possible adaptive processes of the growing child, such procedures should be done at the earliest possible time after the indication becomes evident when benefit and not harm can be done to the individual. As a logical corollary to the studies mentioned, a linear tibial epiphysiotomy seemed an ideal simple method of correcting the

deformity of genu recurvatum by using the normal mechanism of the knee joint to prevent hyperextension and to establish correct alignment of the leg. The fear of epiphyseal injury in this area has been dispelled and neither the epiphyseal growth area nor the joint is disturbed.

A.



B.

Fig. 3.—X-ray in complete extension. *A.* Prior to operation. *B.* Twelve weeks post-operatively.

The procedure used consists of a longitudinal incision over the anterior aspect of the knee and upper half of the tibia. The patellar tendon is sectioned, the joint inspected, and the epiphysis and upper third of the tibia exposed. With a wide thin osteotome, a linear osteotomy is made across the middle of the epiphysis parallel to the articular

surface and extending almost to the posterior cortex of the epiphysis. This is gently pried apart anteriorly and wedge-shaped grafts taken from the tibial crest are inserted firmly to maintain anterior distraction. The recurvatum is corrected entirely at time of surgery. The patellar tendon is sutured, the wound closed, and a long leg cast applied with the knee in moderate flexion. Immobilization for about twelve weeks in children gives firm union.

The case presented is that of a 10-year-old girl with a completely flail leg which has shown remarkable increase in stability following this procedure but which will require additional stabilizing procedures on the foot, ankle, and possibly the hip.

A method of correction of genu recurvatum is presented, using the normal physiologic knee-joint mechanism to block hyperextension by rigid structures, which is performed during the growth period, thus obviating long-continued brace use and increase to more severe deformity during the wait for epiphyseal closure.

REFERENCES

1. Brantigan, O. C., and Voshell, A. F.: The Mechanics of the Ligaments and Menisci of the Knee Joint, J. Bone & Joint Surg. 23: 44, 1941.
2. Brett, A. L.: The Operative Treatment of Genu Recurvatum, Am. J. Surg. 43: 466, 1939.
3. Siegling, J. A.: Growth of the Epiphyses, J. Bone & Joint Surg. 23: 23, 1941.

BLASTOMYCOSIS OF BONE

A Review of 63 Collected Cases, of Which 6 Recovered*

Robert Randolph Jones, Jr., M.D., and Donald S. Martin, M.D.,
Durham, N. C.

(From the Departments of Surgery, Bacteriology and Medicine, Duke University School of Medicine and Duke Hospital)

IN REVIEWING the literature on generalized blastomycosis we have been able to collect 63 cases which showed evidence of bone involvement. Six of these patients recovered after treatment, 3 were not followed sufficiently long to determine their end result, and 53 died of the disease. The detailed case report accompanying this article (page 939)[37] records the history of a seventh patient with bone blastomycosis who was cured after prolonged treatment. Because of the usually poor therapeutic results, we believed it of interest to summarize our present knowledge of this type of infection and to outline certain studies which we have found valuable in the diagnosis, prognosis, and treatment of the disease.

Although the cutaneous type of blastomycosis is familiar to most physicians, the generalized form of the disease is less easily recognized unless it begins with characteristic skin lesions. However, the first signs of infection may be the presence of abscesses in the subcutaneous or deeper tissues. These lesions may resemble either the tuberculous-like "cold" abscess or may be of the acute pyogenic inflammatory type. More commonly the initial symptoms are pulmonary, characterized by the development of a cough productive of small amounts of mucoid sputum. Pleural pain may be the presenting symptom. In 13 patients with bone involvement the primary complaint was arthritic pain in the back or about the joints of the extremities. In 2 cases with bone lesions the initial diagnosis was "articular rheumatism."

In the majority of cases the course of the disease is that of a chronic febrile illness with progressive loss of weight and strength, a moderate secondary anemia, and leucocytosis. The pulmonary symptoms may dominate the picture, the patients having cough, varying amounts of sputum, hemoptysis, or pleural pain. Often there occurs progressive development of soft tissue abscesses with or without bone involvement. In allergic patients these abscesses may develop very rapidly, show signs of acute inflammation, and contain a bloody tenacious exudate. If the degree of allergy is less marked, the "cold" abscesses contain thick purulent material. If these break through the skin or are drained, they frequently lead to the formation of chronic sinuses which drain a thin yellow pus. The foci of infection in the bones of the extremities

*Aided by a grant of the John and Mary R. Markle Foundation.
Received for publication, March 6, 1941.

(Table I), if located near the epiphyseal lines, may extend into joints and form pyarthroses which in turn may drain to the surface through chronic sinuses. Paravertebral or psoas abscesses may form from extension of spine lesions (Table I). Usually the patient succumbs with

TABLE I

DISTRIBUTION OF BONE AND JOINT LESIONS IN 63 REPORTED CASES OF GENERALIZED BLASTOMYCOSIS

LOCATION	NO. OF CASES	LOCATION	NO. OF CASES	LOCATION	NO. OF CASES
Vertebra*	25	Shoulder	1	Hip	3
Skull	21	Elbow	7	Knee	11
Ribs	19	Ulna	4	Tibia	16
Sternum	8	Radius	2	Fibula	6
Clavicle	4	Carpus	10	Patella	3
Scapula	2	Metacarpals	5	Tarsus	12
Pelvis	5	Phalanges	3	Metatarsals	10
Humerus	4	Femur	5	Toes	3

*Paravertebral abscesses were present in 14 cases.

a widespread infection involving not only his skin, soft tissues, lungs, and bones but also the lymph nodes, spleen, liver, and kidneys. In some cases the central nervous system, prostate, heart, and peritoneum have been affected.

Our present concepts of the gross and microscopic pathologic changes in this disease are based largely on Stober's[54] description of the necropsy findings in a large series of cases reported from Chicago. The skin and respiratory tract are the chief portals of entry, and from either site there is a marked tendency for the disease to spread by direct extension or by contiguity of tissue. It is well to note here that two of Stober's cases developed systemic blastomycosis directly following curettement of skin lesions. The pulmonary infection appears first in the bronchi and these lesions spread to become associated with bronchopneumonia in the adjacent lung. The pleura, the pericardium, and the mediastinal lymph nodes may be involved by lymphatic extension from the pulmonary focus. Having entered the blood stream from the lung or the skin, the organisms may be disseminated throughout the body to produce multiple metastatic foci. These, in their turn, may cause further blood stream infection and reinfection of the lungs and other tissues. By this means the skin, the subcutaneous tissue, the muscles and bones, and all the important viscera may be involved.

The tissue reaction to the presence of the organism may be quite variable. Usually the infected areas show round-cell infiltration, not infrequently associated with polymorphonuclear leucocytes, or giant cells or both. However, blastomycetes may be found in tissues showing no histologic change, or the only alteration noted may be small areas of necrosis. Extensive necrosis with abscess formation is common. The typical gross lesions of the disease are the cutaneous ulcers, the deep and superficial abscesses, and the tubercle-like nodules in the viscera.

In bone the infection may be a localized or a diffuse osteomyelitis, a periostitis, or, if a joint is involved, an arthritis. In the long bones the primary focus usually is found at the epiphyseal line and at times the areas of bone destruction resemble infarcts. Microscopic sections show many fungi invading the marrow compartments with the usual cellular reaction, necrosis of the marrow cells, and bone destruction. As the bone partitions disappear, the separate foci may become confluent and form abscesses with separation of sequestra. The joint usually is infected by extension from a focus in adjacent bone through the synovium or cartilage.

The clinical diagnosis of blastomycosis may be suspected from the history and the physical findings. However, a similar picture can be produced by infections with other fungi, tuberculous osteomyelitis, and tertiary syphilis of bone. One of our patients, with lesions of the chest wall and ulna, was thought to have an Ewing's sarcoma until further studies disproved this impression. To establish an unequivocal diagnosis, the clinical impression must be supplemented by laboratory studies.

The isolation and identification of *Blastomyces dermatitidis* from infected secretions or exudates is proof of infection and should be attempted in all cases. The characteristic double-contoured organisms usually can be seen by direct microscopic examination of unstained material and the diagnosis can be confirmed by finding the organisms in fixed tissue biopsy sections stained with hematoxylin and eosin. Tissue examination and cultures, however, are time consuming and we believe that aspiration, drainage, curettage and biopsy often are best deferred until the patient's allergic reaction has been determined by skin tests with a vaccine made from heat-killed Blastomyces. This test and the complement fixation test to be described are also of diagnostic value.

The skin tests are done with a heat-killed vaccine. This vaccine is prepared by suspending, in sterile saline solution, the yeastlike organisms from a culture of *Blastomyces dermatitidis* grown on blood agar at 37° C. This suspension is centrifuged in a Hopkin's tube and the sediment suspended in enough saline solution to make a 1:1,000 dilution by volume. The standardized suspension is heated to 60° C. for four hours and tested for sterility by heavily inoculating a blood agar slant and incubating at 37° C. for at least ten days. Tricresol, 0.35 per cent, is added as a preservative. This material is used for skin testing by injecting 0.1 c.c. intracutaneously. Usually an area of erythema appears about the site of injection within fifteen to twenty minutes. This reaction is not specific and is found in patients having pulmonary disease of other types. The characteristic positive reaction, beginning after twelve to twenty-four hours and reaching a maximum in two to four days, resembles closely a positive tuberculin reaction. In very allergic patients a sterile abscess may form at the site of inoculation. The occurrence of a

positive reaction may be taken as presumptive evidence of the presence of a blastomycotic infection and this diagnosis is strengthened further by finding of complement fixing antibodies in the serum of the patient.

The complement fixation test specific for *Blastomyces dermatitidis* has been described by one of us (D. S. M.),[36] and can be done in any laboratory equipped to do blood Wassermann reactions. The proportions of material and reagents are the same as used in the Wassermann test except for the substitution of a fungus suspension for the beef-heart antigen. Both of these procedures, i. e., the test for sensitivity to heat-killed Blastomyces vaccine and the complement fixation test, can and should be carried out as initial studies on patients suspected of having blastomycosis.

When reviewing the reported cases of blastomycosis, one frequently encounters instances where the diagnosis is based on the finding of the typical double-contoured round or oval bodies in secretions or exudates. These organisms should always be searched for, although from a diagnostic viewpoint the demonstration of organisms *Blastomyces dermatitidis* in secretions or exudates should not be considered unequivocal proof of blastomycosis. Benham has emphasized the fact that other fungi causing generalized lesions may appear as rounded bodies in tissue fluids. Some physicians, unfamiliar with the appearance of the fungus, have had some difficulty in distinguishing between these organisms and fat globules, disintegrating white blood cells and artefacts in sodium hydroxide preparations.

In addition to these studies, it is important to obtain roentgenograms of the chest in all cases of suspected infection because the lungs are the most common portal of entry of the fungus. Roentgenograms also may be made of any bone thought to be involved by the infection and particular attention should be paid to the possibility of spine lesions in patients who complain of backache. Plates should be taken at four- to six-week intervals to follow the progress of the bone lesions. In the case of a solitary bone lesion, it may be difficult for the roentgenologist to differentiate between tuberculous osteomyelitis, a primary osteoclastic tumor (such as Ewing's sarcoma and myeloma), and gumma of bone. However, when there are multiple bone lesions, a roentgenologic diagnosis of blastomycosis can be suspected. Well-localized, sharply defined destructive processes in the metaphyses, when multiple, suggest blastomycosis rather than the other conditions listed above. It has been stated that roentgenologic differentiation between blastomycosis and coccidioidal granuloma is difficult if not impossible.

As in any chronic debilitating illness, general hygienic measures are of first importance in the treatment of patients having generalized blastomycosis. Patients having this disease usually are individuals whose economic status is poor and who have been on an inadequate diet for months or years. Bed rest and an adequate diet are essential. The

diet should be supplemented by the administration of cod liver oil, large quantities of orange or tomato juice, and brewers' yeast. Anemia, if present, should be treated appropriately. The administration of potassium iodide is best deferred and the care of the local lesions should be purely palliative and conservative until the diagnosis has been established and the patient's allergic status determined.

The skin test with Blastomyces vaccine serves not only as a diagnostic procedure but also as a means of determining whether or not the patient should be desensitized. If the vaccine produces a sterile abscess, desensitization should be started with a dose of 0.1 c.c. of a 1:1,000 dilution of the vaccine (a 1:1,000,000 dilution of the original material). This is administered no more frequently than every other day and the dosage is kept below the point of causing a local or general reaction. Less sensitive patients can be started with a higher initial dosage. After the degree of allergy has been reduced, as judged by skin testing, iodides may be administered cautiously. We usually give a saturated solution of potassium iodide; beginning with 3 drops t. i. d. and increasing 1 drop per dose every day until tolerance is reached. In the case of an exacerbation of symptoms following the taking of iodides, the drug should be discontinued promptly and further attempts made to desensitize the patient. Complete desensitization is not thought necessary; however, the Blastomyces vaccine should be given until iodides are tolerated without unfavorable reaction. Beyond this the patient's need for the repeated administration of vaccine may be prescribed according to the judgment of the physician.

The care of the local lesions is best limited to conservative measures until desensitization is well under way and the administration of iodides has been started. Aspiration of deep or superficial abscesses may be done early when this procedure is necessary to establish a diagnosis, but it is best deferred until after medical treatment has been given. Open drainage of abscesses, curettage of ulcers or sinuses, and sequestrectomy are thought to be contraindicated in generalized blastomycosis by some observers. We believe that these procedures may be necessary at times, but that they should not be done until partial desensitization has been accomplished and iodides have been administered. Although amputation has been reported as curing at least one patient and may be indicated when the bones of the foot and ankle have been extensively damaged, the generalized nature of the infection should be kept in mind and this procedure used only as a last resort. In our experience we have encountered one patient with blastomycosis of bone who showed no evidence of skin sensitivity to Blastomyces vaccine. The treatment in this case is recorded in a subsequent report (page 939).[37]

Potassium iodide was given to all six patients who recovered from bone blastomycosis (Table II). Three of these also received heliotherapy which was believed to be beneficial. Two patients were given

TABLE II

CASES OF GENERALIZED BLASTOMYCOSIS WITH BONE LESIONS WHICH RECOVERED

1. Herrick:[23] White, female, 24 years of age. Onset with rheumatic pains in left gluteal region. Subsequently developed seventy-nine different lesions which in some instances, as in the case of the fingers, destroyed bone. Treated with potassium iodide by mouth and drainage of the local foci. No improvement until moved residence to California and lived out-of-doors. Recovery after an illness of three years' duration.
2. Boughton and Stober:[6] White, male, 29 years of age. Onset with pain in the chest, cough, fever, and weakness. The dorsum of the feet became swollen and tender and the initial diagnosis was "rheumatism." Total of twenty-four lesions developed, including multiple abscesses and foci in the upper and lower ends of the right tibia. Treated first with potassium iodide for two and one-half months but without improvement until blastomyces vaccine given. The latter caused inflammatory reaction about lesions but was followed by healing. Roentgenograms showed evidence of bone healing and recovery after further treatment with potassium iodide and vaccine. Reported as apparently well eighteen months after the onset of first symptoms.
3. Marshall:[35] White, female, 50 years of age. Onset with generalized weakness, loss of weight, and swelling of the right foot. Skin lesions appeared followed by afternoon elevations of temperature. Roentgenograms showed osteomyelitis of the metatarsals, osteoporosis of the cuboid, astragalus, and both malleoli. Treated with x-ray therapy over the skin lesions, potassium iodide, and sun baths. Gradual recovery occurred although several new nodules appeared after starting treatment. It was thought that the daily sun baths were largely responsible for recovery, although one of the attending physicians ascribed the improvement to x-ray therapy. After a winter in Florida, patient was apparently well one year after the onset of the infection.
4. Gillies:[19] White, male, 15 years of age. Onset with sore throat, hoarseness, cough, expectoration, and loss of weight. About the same time the left foot became swollen and three weeks later a draining sinus developed. Roentgenograms of the chest showed an infiltration of the left lung and films of the foot revealed an osteomyelitis of the tarsus. Six months later the foot was amputated and blastomycetes found in the specimen. Meanwhile ulcers had developed on the right arm and leg. Potassium iodide was started nine months after onset and heliotherapy intensified. The patient was apparently well one year after the onset of symptoms and has remained so for six years.
5. Bergstrom, Nugent, and Snider:[4] Colored, male, 49 years of age. Onset with a "boil" on his leg. Multiple skin lesions developed and roentgenograms showed foci in the bones of one hand, in the left maxilla, and in the bones of both feet. Treated with neoarsphenamine, potassium iodide in milk, antimony and potassium tartrate intravenously, and with 3 c.c. of colloidal copper intramuscularly every five days for twenty doses. Five per cent iodine ointment was used on the local lesions. No improvement until the administration of the colloidal copper intramuscularly, but thereafter no new lesions appeared and those present began to heal. Ten months after discharge all lesions had healed except a sinus over one heel.
6. Martin and Smith:[39] White, female, 27 years of age. Onset with a fall causing a back injury and a broken arm. Shortly thereafter developed a cough with hemoptysis and had an elevated temperature. Hospitalized with a pulmonary infection diagnosed as blastomycosis. Improved under administration of blastomyces vaccine, potassium iodide, and the chest lesion cleared up. About this time was found to have blastomycosis of the uterus and tubes and these organs were removed.[21] Subsequently there developed a destructive process in the twelfth thoracic vertebra followed by a paraplegia. This improved following laminectomy and further courses of blastomyces vaccine and potassium iodide. Her complement fixation test became negative and she has remained clinically well for five years.

Blastomyces vaccine with apparent benefit and in one case x-ray therapy was thought to have been responsible for the improvement. There is a recent report of a patient who recovered after treatment with potassium iodide, antimony, and potassium tartrate intravenously, and 3 c.c. of colloidal copper intramuscularly every five days for twenty doses. The last drug was believed to have caused the patient's improvement. The local application of a copper sulfate solution would appear to be of little value in cases of the generalized disease. Although studies have suggested the possible value of intravenous gentian violet in treating this infection we have found no reported instance of its clinical trial.

The prognosis of the majority of patients having blastomycosis with bone lesions is poor, especially in those individuals who have a high titer of complement fixing antibodies. Undoubtedly there are many patients who have recovered from this disease whose case records have not been reported in the literature. It is to be hoped that in the future more cases of clinical cures will be recorded and that a better knowledge of the factors responsible for recovery can be obtained.

SUMMARY

1. In a review of the 63 reported cases of bone blastomycosis, there were found 6 patients who recovered from the disease.

2. The locations of the bone lesions are tabulated and a résumé given of the cases which recovered.

3. Our present knowledge of this infection is summarized.

4. The problem of diagnosis is discussed and the suggestion made that patients having bone lesions be partially desensitized to Blastomyces vaccine before beginning treatment with either iodides or surgery.

REFERENCES

1. Bassoe, P.: J. Infect. Dis. **3**: 292, 1906.
2. Bechtel, R. C., and LeCount, E. R.: Arch. Int. Med. **13**: 609, 1914.
3. Benham, R. W.: Arch. Dermat. & Syph. **30**: 385, 1934.
4. Bergstrom, V. W., Nugent, G., and Snider, M. C.: Arch. Dermat. & Syph. **36**: 70, 1937.
5. Boughton, T. H., and Clark, S. N.: Arch. Int. Med. **13**: 594, 1914.
6. Boughton, T. H., and Stober, A. M.: Arch. Int. Med. **13**: 599, 1914.
7. Churchill, T., and Stober, A. M.: Arch. Int. Med. **13**: 568, 1914.
8. Cole, W. H.: Ann. Surg. **80**: 124, 1924.
9. Cooper, C. N.: J. Iowa M. Soc. **21**: 119, 1931.
10. Coupal, J. F.: Internat. Clin. **4**: 1, 1924.
11. Craig, W. M., Dockerty, M. B., and Harrington, S. W.: South. Surgeon **9**: 759, 1940.
12. D'Aunoy, R., and Beven, J. L.: J. Lab. & Clin. Med. **16**: 124, 1930.
13. Dickson, E. C.: Arch. Int. Med. **16**: 1028, 1915.
14. Dowling, G. B., and Elsworthy, R. R.: Proc. Roy. Soc. Med. **19**: 4, 1925.
15. Eisendrath, D. N., and Ormsby, O. S.: J. A. M. A. **45**: 1045, 1905.
16. Eisenstaedt, J. S., and Boughton, T. H.: Arch. Int. Med. **13**: 617, 1914.
17. Garr, C. C.: Surg., Gynec. & Obst. **41**: 490, 1925.
18. Gaspar, I., Fenstermacher, W. A., and Lingeman, L. R.: Radiology **18**: 305, 1932.
19. Gillies, M.: Canad. M. A. J. **29**: 183, 1933.
20. Good, R. W.: U. S. Vet. Adm. M. Bull. **8**: 490, 1932.

21. Hamblen, E. C., Baker, R. D., and Martin, D. S.: Am. J. Obst. & Gynec. **30:** 345, 1935.
22. Harding, D. B., and Garr, C. C.: South. M. J. **26:** 315, 1933.
23. Herrick, J. B.: J. A. M. A. **49:** 328, 1907.
24. Hill, H. P., and Dickson, E. C.: California J. M. **12:** 120, 1914.
25. Howes, W. B., and Morse, P. F.: Boston M. & S. J. **185:** 315, 1921.
26. Hurley, T. D.: J. Med. Research **33:** 499, 1915.
27. Iglauer, S.: Ann. Otol., Rhinol. & Laryngol. **39:** 56, 1930.
28. Irons, E. E., and Graham, E. A.: J. Infect. Dis. **3:** 666, 1906.
29. Jones, T. B.: Surg., Gynec. & Obst. **50:** 972, 1930.
30. Krost, R. A., Stober, A. M., and Moes, M. J.: Arch. Int. Med. **13:** 557, 1914.
31. Le Count, E. R., and Myers, J.: J. Infect. Dis. **4:** 187, 1907.
32. Lewison, M., and Jackson, H.: Arch. Int. Med. **13:** 575, 1914.
33. Maner, G. D., and Hammack, R. W.: California & West. Med. **32:** 87, 1930.
34. Marquardt, C. R.: J. Urol. **25:** 531, 1936.
35. Marshall, C. H.: Memphis M. J. **6:** 218, 1929.
36. Martin, D. S.: J. Infect. Dis. **57:** 291, 1935.
37. Martin, D. S., and Jones, R.: SURGERY **10:** 939, 1941.
38. Martin, D. S., and Smith, D. T.: J. Lab. & Clin. Med. **21:** 1289, 1936.
39. Martin, D. S., and Smith, D. T.: Am. Rev. Tuberc. **39:** 275, 1939.
40. McKenty, F. E., and Morgan, D.: Ann. Surg. **61:** 513, 1915.
41. Medlar, E. M.: Am. J. Path. **3:** 305, 1927.
42. Michelson, I. D.: J. A. M. A. **91:** 1871, 1928.
43. Montgomery, F. H., and Ormsby, O. S.: Arch. Int. Med. **2:** 1, 1908.
44. Montgomery, H.: M. Clin. North America **14:** 651, 1930.
45. Myers, H. J., and Stober, A. M.: Arch. Int. Med. **13:** 585, 1914.
46. Raiford, T. S.: Johns Hopkins Hosp. Bull. **51:** 61, 1932.
47. Ravogli, A.: Acta dermat.-venerol. **6:** 281, 1925.
48. Riley, F. B., and Le Count, E. R.: Arch. Int. Med. **13:** 614, 1914.
49. Ryerson, E. W.: Am. J. Orthop. Surg. **6:** 79, 1908.
50. Rypins, E. L.: Radiology **22:** 77, 1934.
51. Schwartz, V. J.: Arch. Ophth. **5:** 581, 1931.
52. Shaffner, P. F.: Arch. Int. Med. **13:** 621, 1914.
53. Shepherd, F. J., and Rhea, L. I.: J. Cutan. Dis. **29:** 588, 1911.
54. Stober, A. M.: Arch. Int. Med. **13:** 509, 1914.
55. Toepel, T.: J. A. M. A. **93:** 32, 1929.
56. Wade, H. W., and Bel, G. S.: Arch. Int. Med. **18:** 103, 1916.

SYSTEMIC BLASTOMYCOSIS

Report of a Case with Unusual Immunologic Findings, Well Two Years After Onset*

Donald S. Martin, M.D., and Robert Randolph Jones, Jr., M.D.,
Durham, N. C.

(From the Departments of Medicine, Bacteriology, and Surgery, Duke University School of Medicine and Duke Hospital)

INTRODUCTION

THE treatment of blastomycosis (American form) varies with the individual patient, depending upon the extent of the infection, the degree of allergy developed by the patient, and the locality and nature of the individual lesions. The following case is reported because the patient presented an immunologic picture markedly different from that usually seen in blastomycosis, which necessitated a radical departure from the treatment usually used in this disease.

CASE REPORT

H. M. M. (History No. A5847), a white farmer, 30 years of age, was admitted to Duke Hospital on Aug. 8, 1938, complaining of pain in the left elbow and forearm of six weeks' duration.

Family History.—The patient's father, mother, six brothers, and three sisters were well.

Past History.—The patient's general health had been good. He had had measles and pertussis in childhood and had had three attacks of influenza since 1918. Four years prior to the onset of the present illness he had had a chronic cough which lasted for several months. There was no hemoptysis, chest pain, or fever during this illness.

Present Illness.—Eleven weeks before admission to the hospital, the patient noticed a small area of tenderness over the left eleventh rib which became increasingly painful. After three weeks a small swelling appeared which was incised by his physician with the evacuation of a small amount of sterile pus. The exposed rib was curetted and the wound has remained as an indolent cavity. Six weeks before hospitalization a swollen, tender spot developed over the left ulna just distal to the elbow joint. This swelling increased in size for about ten days and the patient noticed that movement of the elbow caused pain. Ten days before he entered the hospital this area was incised with evacuation of some necrotic bone. The pus from this wound was reported also as showing no growth of pyogenic organisms. Both wounds continued to drain and the elbow has remained painful.

Physical Examination.—The patient was a 30-year-old, undernourished white farmer, with normal temperature, pulse, and respirations. There were no abnormalities except for the two areas described. Over the left eleventh rib there was a cavity, 6 by 3 cm. in size, lined by indolent granulation tissue. The rib was not exposed at the bottom of the wound. The left elbow was markedly swollen

*Aided by a grant of the John and Mary R. Markle Foundation.
Received for publication, March 6, 1941.

Fig. 1.—*1*, Roentgenologic appearance of elbow lesion on Aug. 20, 1938, before iodide therapy was begun; *2*, appearance of bone lesion on Oct. 4, 1938; *3*, appearance of bone lesion at time of discharge, May 1, 1939; *4*, appearance of elbow lesion on return visit to the hospital, Aug. 14, 1940.

and any motion of the joint caused pain. Over the proximal end of the ulna, there was an incision 6 cm. in length which was lined with necrotic tissue and drained bloody pus.

Accessory Clinical Findings.—Hgb., 98 per cent; R.B.C., 4,480,000; W.B.C., 10,300. Differential: P.M.N. 86 per cent; L.L., 3 per cent; S.L., 8 per cent; E., 1 per cent, M., 2 per cent. Urine: acid, specific gravity, 1.023; albumin, negative; sugar, negative; microscopic examination showed only an occasional W.B.C.; Wassermann, negative; stool, negative. Blood Chemistry: N.P.N., 36; Ca, 8.6; P, 3.2; refractive index, 1.350.

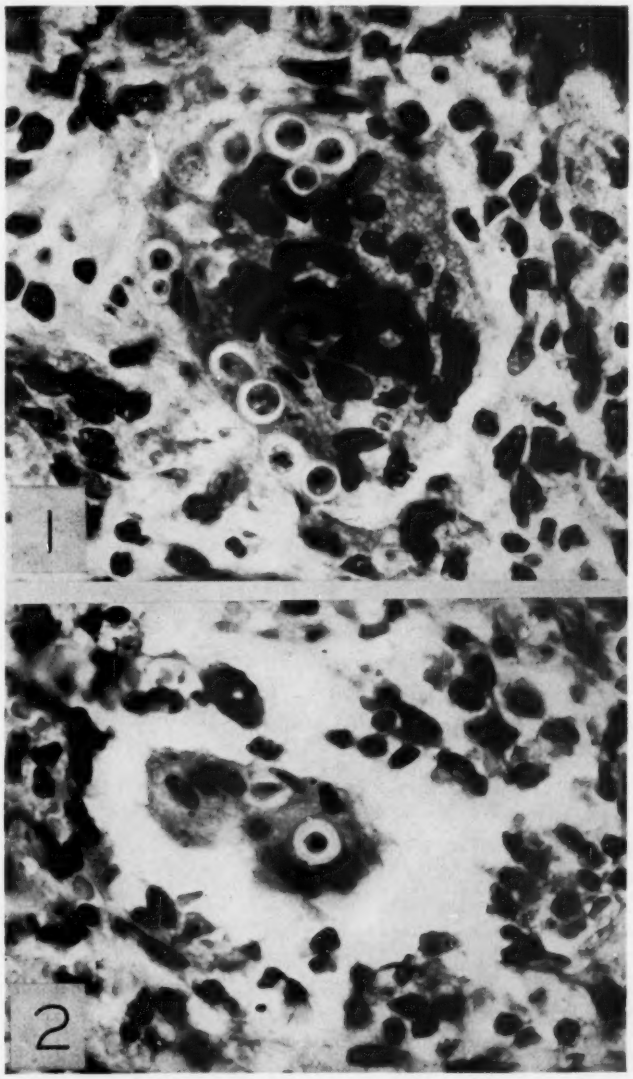


Fig. 2.—*1*, Biopsy section of skin from another case showing the usual appearance of *Blastomyces dermatitidis; 2*, Biopsy section of skin from present case to illustrate the difference in size of the double-contoured wall. For comparison, each of these sections was cut from blocks, mounted, and stained under identical conditions.

Roentgenograms showed a destructive process in the left eleventh rib, in the posterior axillary line, and in the left olecranon (Fig. 1, *1*). The findings in both sites suggested osteomyelitis. Fluoroscopy and films of the chest showed a slight increase in the peribronchial markings bilaterally and a slight thickening of the pleura at the left apex.

Bacteriologic Studies.—*Staphylococcus aureus* was grown from the rib lesion, but cultures for bacteria from the elbow region showed no growth. Cultures for tubercle bacilli were negative. There was no reaction to the intracutaneous injection of old tuberculin diluted 1:10,000.

Mycologic Studies.—Budding fungi were found in direct smear and in sections of material obtained by biopsy. The appearance of these organisms differed somewhat from the usual *Blastomyces dermatitidis* in that the double-contoured peripheral membrane of the fungus cells seemed much wider than usual (Fig. 2, *1* and *2*). Although there was the definite impression that the organisms were true Blastomyces, several observers suggested that the fungus might prove to be a Cryptococcus. However, cultures of the fungus from this case on Sabouraud's medium at room temperature and on blood agar at 37° C. showed no essential differences from the usual Blastomyces isolated from cases of American blastomycosis.[1] There was also no detectable difference antigenically between this strain and other strains of Blastomyces when tested for combining capacity with an anti-Blastomyces rabbit serum.

Course in the Hospital.—The wounds were curetted the day after admission. The cavity in the ulna was found to extend into the elbow joint, but the eleventh rib at operation was covered by a compact layer of granulation tissue.

Skin tests to a heat-killed vaccine and three fractions of *Blastomyces dermatitidis* were done on Aug. 12, 1938, four days after admission. No reaction was obtained with any of these substances. In view of the negative skin test to *Blastomyces dermatitidis* and the questionable diagnosis of cryptococcosis, the patient was injected intracutaneously with 0.1 c.c. of heat-killed vaccines prepared from three strains of pathogenic cryptococci. None of these was positive. Since the patient exhibited no signs of hypersensitivity to the fungus, potassium iodide was given by mouth, starting with three drops t. i. d. and increasing the dose at a rate of three drops per day. He was given, also, a high caloric, high vitamin diet. The wounds were treated with warm saline fomentations and the lesions cauterized on several occasions. Under this therapy the rib area improved, but the bone lesion in the elbow grew worse. By Sept. 23, 1938, forty-six days after admission, his iodide dosage had reached 114 drops per day, but he had gained only 0.35 kg. in spite of his enhanced diet. Except for a temperature of 38.5° C. on one occasion, he had only a low-grade fever. His white count varied between 6,350 and 10,450 (Fig. 3).

After six weeks' observation it was obvious that a more radical form of treatment was necessary to save the patient's arm. On Sept. 29, 1938, 0.1 c.c. of undiluted anti-Blastomyces rabbit serum was injected intracutaneously. Normal rabbit serum was used as a control. The anti-Blastomyces rabbit serum caused, within fifteen minutes, an edematous area 12 by 19 mm. surrounded by a zone of erythema 46 by 70 mm. During the same interval of time the control serum produced a raised area only 11 by 12 mm. and there was no erythema. This test is similar to that described by Foshay[2] except that 0.1 c.c. of undiluted serum was used instead of 0.04 c.c. of a 1:10 dilution as recommended by him.

Several subcutaneous injections of small doses of rabbit serum were given, the patient receiving 0.25 c.c. on Sept. 27, 0.5 c.c. on Sept. 28 and 29, and 1 c.c. on Sept. 30. The last dose which was injected into the left upper arm midway between the elbow and shoulder resulted in an intense local reaction which was greatest around the elbow. There was some erythema and swelling as high as 5 cm. above the site of injection, but the whole region of the elbow was greatly swollen and extended well down into the forearm. Because of the severity of the reaction, the dosage was cut to 0.1 c.c. on Oct. 2 and 0.05 c.c. on Oct. 4. There was no febrile reaction following the serum injections, but the white count rose to 12,000. Dur-

ing the following two weeks the patient gained 1.65 kg. in weight. An x-ray on Oct. 4, 1938 (Fig. 2, *2*), showed that bone destruction had increased considerably under iodide therapy.

At this time amputation of the left arm was considered, but the patient demurred and he received 1,200 r. units of deep x-ray therapy from Oct. 20 to 25. The elbow lesion failed to improve clinically, but there was no evidence of a spread of the infection. The low-grade fever slowly subsided as did the white count, which had been elevated following the serum injections (Fig. 3). It was felt that the introduction of maggots might remove some of the necrotic tissue and increase drainage and these were introduced on Nov. 9 and at intervals until Nov. 23. During this time considerable healing of the bone was demonstrated by x-ray. There were several bouts of fever during this treatment. Three weeks after maggots were first introduced, the patient developed multiple furuncles, hemolytic *Staphylococcus aureus* bacteremia, and a severe upper respiratory infection. Potassium iodide was discontinued Dec. 29. He was severely ill for three months, necessitating surgical treatment for the abscesses, several courses of sulfanilamide and sulfapyridine, staphylococcus antitoxin, nicotinic acid, thiamin chloride, liver, and transfusions. Repeated examinations of the elbow lesion and of numerous abscesses and the sputum failed to demonstrate Blastomyces, and it was apparent that the fungus infection had been brought under control before the onset of the severe bacteremic infection with *Staphylococcus aureus*.

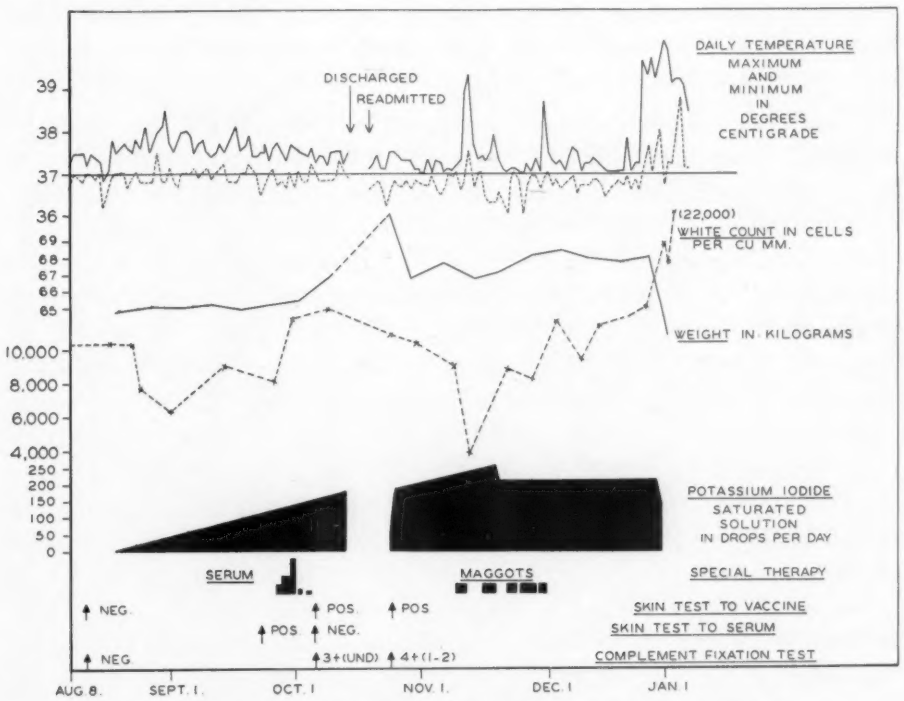


Fig. 3.—Chart illustrating the patient's course in the hospital.

Following the injections of anti-Blastomyces serum, there was a complete reversal of the immunologic picture. On Oct. 5, 1938, the Foshay test was repeated and the results showed no increase in reaction to the anti-Blastomyces serum as compared with the normal rabbit serum control. A skin test on Oct. 5 to a filtrate of Blastomyces gave a markedly positive reaction within twenty-four hours, but the area of erythema had completely disappeared within forty-eight hours. This

same type of reaction is obtained in allergic patients when tested with a purified carbohydrate fraction of the fungus.[3] The patient's serum, previously negative for complement fixing antibodies, gave a weakly positive reaction on Oct. 6 (3+ in undiluted serum) and a stronger reaction on Oct. 21 (4+ in 1-2 dilution of serum). The complement fixation test was negative at the time of discharge on April 3, 1939, but a skin test to the same filtrate again resulted in a positive twenty-four-hour reaction. The extent of reaction was less than that previously found.

The patient was discharged from the hospital on April 4, 1939, with the wound on the elbow completely healed. An x-ray of the bone on May 1, 1939, showed considerable filling in of the bone cavity (Fig. 1, *3*). He was last seen on Aug. 14, 1940, and had no more symptoms. He had gained approximately 15 kg. in weight and had complete range of motion of his elbow. An x-ray at this time (Fig. 1, *4*) showed healing of the bone except for a fracture line across the olecranon. It was felt that this line of decreased density represented healing of the cavity with fibrous tissue rather than a true fracture, since the patient had complete function of the joint and there were no physical signs or symptoms suggestive of fracture.

DISCUSSION

It is very difficult to evaluate the effects of specific forms of therapy in a disease such as blastomycosis because the limited number of patients seen by any individual or clinic makes statistical analysis of no value. Furthermore, like tuberculosis, each case presents a different problem and must be treated individually.

In this patient evaluation of treatment is especially difficult, since he received iodides, deep x-ray therapy and antiblastomycotic rabbit serum in addition to surgical procedures, such as curettement, cauterization, and application of maggots into the wound. The results of treatment in this patient, as compared with our experiences with other patients with this disease,[4] have suggested to us certain possibilities which are outlined below.

Iodides have been shown by us[4] to be potentially harmful to patients who have developed a high degree of allergy to the infecting fungus. This patient, with no evidences of hypersensitivity to the fungus, theoretically should have responded well to the drug. However, during the six-week period of iodide administration he continued to have low-grade fever, failed to gain significantly in weight, and the local lesion in his elbow became worse. The appearance of the fungus in smears suggested either a different form of the fungus or a peculiar reaction of the host cells to the fungus. This has its counterpart in other fungus infections, actinomycosis in particular, in which the club-shaped swellings of the mycelia in the periphery of the sulfur granules are thought to represent the results of an interaction between the host and the parasite, since these swellings are rarely observed in culture. It is not certain whether or not *Blastomyces dermatitidis,* under certain conditions, may form a capsule in animal tissues or whether the capsular appearance represents only an exaggeration of the usual thick-walled membrane. However, in a case reported by Rewbridge, Dodge, and Ayers,[5] the authors were so

impressed by the morphologic appearance of the fungus in the lesion that they considered the organism to be a new species, *Endomyces capsulatus*. Cultural studies of this strain of *E. capsulatus* by Benham[6] and in this laboratory[1] have shown no essential differences from the usual strains of *Blastomyces dermatitidis* isolated from numerous cases of American blastomycosis.

The positive Foshay test further suggests that the fungus was producing some antigenic substance which may have masked or prevented the development of a skin reaction to the intracutaneous injection of dead organisms or filtrates of the organism. This substance presumably inhibited also the demonstration of antibodies in the serum of the patient. The severe local reaction around the elbow following the injection of 1.0 c.c. of anti-Blastomyces rabbit serum emphasized that production of this hypothetical antigenic material was most intense in the area of infection. The apparent benefit following the injection of only 2.4 c.c. of serum, with a complete reversal of the immunologic picture, may be interpreted by assuming that this excess material was neutralized by the antibodies in the rabbit serum, allowing the host's cells, aided by iodides, to attack the invading fungi. The positive complement fixation reactions could not have been explained by the passive transfer of antibodies because of the small amount of serum injected. The observation that the test became more strongly positive three weeks later suggested that the patient previously had built up a certain degree of resistance to the fungus but that evidences of this resistance were masked by the local production of this soluble antigen. This substance may have prevented local healing of the lesion and caused the reversal of the usual findings of hypersensitivity to the fungus and the presence of serum antibodies.

The role of hypersensitivity to bacteria or bacterial products in infections is debatable. It seems that a certain amount of allergy is desirable in localizing an infection but that too great a degree of allergy is harmful because of the severity of the reaction following a spread of the infection or the liberation of bacterial products. In none of our previous cases was desensitization with Blastomyces vaccine complete and in this case the mild degree of allergy which developed after serum treatment did not seem to be sufficient to warrant discontinuation of iodides.

The role of maggots in the ultimate cure of this patient was felt to be due entirely to their action in removing necrotic tissue and maintaining of open sinuses for drainage. The possibility that maggots could have had any direct fungicidal effect was not investigated.

A third factor that must be considered is the effect of the severe staphylococcic infection. It has been shown experimentally by Baker[7] that mice infected intraperitoneally have less marked lesions if the peritonitis is complicated by bacterial infection. It is difficult, however, to believe that the presence of bacterial infection in this patient played a

part in controlling the fungus infection because improvement in the latter occurred before the appearance of abscesses and bacteremia.

SUMMARY

An unusual case of blastomycosis of bone is presented.

After failure to obtain improvement with iodides, this treatment was supplemented by subcutaneous injections of small amounts of immune serum and the introduction of maggots into the local lesion.

The possible effects of these two additional agents in bringing about the ultimate cure of the patient are discussed.

REFERENCES

1. Conant, N. F., and Martin, D. S.: A Comparative Study of Nineteen Strains of *Blastomyces dermatitidis* Gilchrist and Stokes 1898. To be published.
2. Foshay, L.: Intradermal Antiserum Tests: a Bacterial-Specific Response Not Dependent Upon Serum Sensitization but Often Confused With It, J. Allergy **6**: 360-364, 1935.
3. Peck, R. L., Martin, D. S., and Hauser, C. R.: Polysaccharides of *Blastomyces dermatitidis*, J. Immunol. **38**: 449-455, 1940.
4. Martin, D. S., and Smith, D. T.: Blastomycosis. II. A Report of Thirteen New Cases, Am. Rev. Tuberc. **39**: 488-515, 1939.
5. Rewbridge, A. G., Dodge, C. W., and Ayers, T. T.: A Case of Meningitis Due to *Endomyces capsulatus* (New Species), Am. J. Path. **5**: 349-364, 1929.
6. Benham, R. W.: The Fungi of Blastomycosis and Coccidioidal Granuloma, J. Infect. Dis. **30**: 385-400, 1934.
7. Baker, R. D.: Comparison of Infection of Mice by Mycelial and Yeast Forms of *Blastomyces dermatitidis*, J. Infect. Dis. **63**: 324-329, 1938.

LOCAL SULFANILAMIDE THERAPY IN SURGICAL INFECTIONS

J. Ross Veal, M.D., and Roy G. Klepser, M.D.,
Washington, D. C.

(From the Department of Surgery of the Gallinger Municipal Hospital)

THE introduction of the sulfonamides has changed entirely the mode of treatment for many diseases. The adaptation of these new drugs to the therapy of surgical infections has been relatively slow due to the comparatively poor results obtained by their oral and parenteral administration in walled-off pyogenic lesions.

Meleney and Harvey,[1] in 1939, reported a series of 40 chronic undermining ulcers infected with hemolytic streptococci treated with local application of zinc peroxide and the oral administration of sulfanilamide. In the cases with an associated acute cellulitis and lymphangitis they obtained good results. In the more chronic cases, in which there were considerable necrosis, undrained abscesses, and locally decreased blood supply, the sulfanilamide was without effect. Bricker and Graham,[2] also in 1939, found that the oral administration of sulfanilamide retarded the healing processes of clean incised wounds of dogs' stomach. These experiments were later repeated by Taffell and Harvey,[3] who did not demonstrate any abnormality of healing. Key and Burford[4, 5] have stated that they found no inhibition of healing in experimental fractures in rabbits after the local instillation of sulfanilamide at the site of fracture. Jensen, Johnsrud, and Nelson[6] reported 39 cases of compound fractures treated by careful débridement and the local implantation of powdered sulfanilamide. These wounds were then closed. All healed by primary union. Ninety-four similar cases treated in the same manner without sulfanilamide had a total of 29 infections. Campbell and Smith,[7] reporting 54 cases of compound fractures treated with local application of sulfanilamide, did not feel that the incidence of infection was materially reduced in the acute cases. However, they found that the drug greatly reduced the incidence of postoperative infections in cases in which surgery was undertaken in the presence of chronic inflammation. Rapid control of secondary infection in chancroids by the topical application of sulfanilamide powder was first described in 1938 by Fields and Weinstein.[8] Since the advent of the current war several papers have appeared in which the authors claim excellent results from the local use of sulfone drugs in contaminated and infected war wounds.[9-11] Levaditi[12] has reported rapid and effective sterilization of war wounds by the local application of sulfanilamide. Oral administration of the drug in such cases was ineffective.

Received for publication, June 3, 1941.

Considerable material is now available on the bacteriostatic and bactericidal effects of sulfonamides in vitro against the common contaminants of surgical wounds.[13-17] Lawrence[18, 19] has investigated the comparative effects of the various sulfonamide drugs upon cultures of the colon-typhoid-dysentery group. Most of the investigators agree that the maximum bacteriostatic effect is obtained in an aerobic medium.[20-22] Lockwood[23, 24] has recently reported upon the mode of action of these drugs as applied to local bacteriostasis in infected lesions. He believes that they act locally by interfering with the nutritional requirements of certain bacteria, the effect being dependent upon the concentration of the drug and the amount of free peptone available from tissue necrosis. Whether this theory or the anticatalase theory[25, 26] is correct, the need of débridement of all necrotic tissue and the continued local concentration of the drug is paramount. Since 1936 Ravdin[27] has routinely given sulfanilamide parenterally and orally in all cases of acute appendicitis and appendical abscesses. He and his associates report a pronounced lowering of morbidity and mortality rates since initiating this routine. Recently the local intraperitoneal application of sulfanilamide powder to the region of the appendix has been described by Thompson, Brabson, and Walker.[28] In 204 cases of purulent or ruptured appendices they placed 12 Gm. of sterilized sulfanilamide powder into the peritoneal cavity and the muscle layers of the abdominal incision. No toxic effects or local devitalization of tissues was noticed.

During the past year we have treated over 300 infected wounds by the local implantation of sulfanilamide powder.[29] These cases include postoperative wound infections, many types of traumatic wounds, infected burns, compound fractures, leg ulcers, decubitus ulcers, localized abscesses, and carbuncles. The results obtained by this method have been so excellent that it has now largely supplanted all other forms of local treatment of infected wounds in our hospital. The chief advantages are its rapid, effective, and nonirritative action, the simplicity of the dressing care needed, and the comfort afforded the patient. It is also cheap and readily accessible. We have encountered some disadvantages with its use. Most of these disadvantages can be overcome if certain rules are followed. In this communication we wish to record the technique employed and the results obtained in the local treatment of infected wounds with sulfanilamide.

We have endeavored to determine the direct effect of sulfanilamide on the various organisms found in these pyogenic wounds. In a large series of cases smears and cultures were made before beginning the local treatment. At intervals during the period of treatment similar bacteriologic studies were repeated. Biopsies of the edges of the wounds were also taken in a group of 70 cases, showing sections of the tissues before treatment and during the process of healing. In this manner we have obtained a qualitative and, in a sense, a quantitative test of

the action of sulfanilamide upon the local tissue. In the great majority of our cases the smears and cultures showed a mixed flora of bacteria. Chief among these were streptococci, staphylococci, the *Bacillus coli* group, and diphtheroids. An important secondary invader in some cases was *Bacillus pyocyaneus*. After the preliminary bacteriologic and microbiologic studies were completed the wounds were treated by adequate drainage or débridement and the local implantation of sulfanilamide powder. The dose of sulfanilamide introduced was determined by the size of the lesion. A sufficient quantity was used to cover the wound surface completely and to fill all pockets. On the following day the smears and cultures were repeated. There was an immediate diminution in the number of organisms found in the smears and the colonies grown on plated cultures. All of the types of organisms found in these wounds were affected. In those cases in which a new supply of sulfanilamide was not introduced we found that there was usually a reactivation of the bacterial growth. If daily applications of sulfanilamide were made, however, the number of bacteria continued to decline until there was a practical sterilization of the wound. This usually required from five to eight days. Along with the reduction in number of bacteria there was a striking diminution in the amount of exudate. The necrotic odor of some of the wounds was immediately banished. This has been particularly noticeable in the cases of ruptured appendices where it had been necessary to drain the abscess. After the bacterial growth and exudate had been controlled we discontinued the sulfanilamide. In some of the cases the wounds remained clean and healing processes progressed steadily. In others we observed that there was a gradual resumption of the bacterial growth and a return of inflammation. We then resumed the daily instillation of the sulfanilamide. By continuing the application of the drug we maintained control of the infection, but another complication developed. In some cases the healing came to a complete standstill. The granulation tissue appeared dry, anemic, and indolent. As long as the concentrated drug was used the healing was retarded. Biopsies from the lesions at this stage showed very poor vascularization of the granulation tissue. Complete removal of the sulfanilamide was sometimes followed by more abundant granulations and resumption of wound healing. In some cases, however, the invading organisms again became active, and we were once more dealing with an infected wound. It seemed desirable to keep available in the wound some sulfanilamide, yet not enough to hinder healing. We then attempted to use a less concentrated form of the drug after the initial infection had been controlled. Aqueous solutions and oil suspensions proved inadequate,[30] and the incorporation of the drug into various inert ointments was not satisfactory. We then requested the National Drug Co. to prepare for us an ointment combining sulfanilamide and allantoin in a greaseless base. According to Robinson[31] and others[32, 33]

allantoin produces a stimulating effect on indolent granulation tissues by increasing their vascularity. After several trials we found that a combination of sulfanilamide 10 per cent with allantoin 2 per cent in an absorbable glycerinated base did give remarkably good results. Within a few days following the substitution of the ointment in place of the concentrated powdered sulfanilamide the tissues became active and healthy in appearance and the infection remained under control. (Figs. 1 *A*, *B*, and *C*.) In a number of cases the same ointment was used without including allantoin in the formula. Although these wounds healed and lacked the indolent phase characteristic of full-strength sulfanilamide, the growth of granulation tissue was not as rapid or as freely bleeding as when allantoin was used.

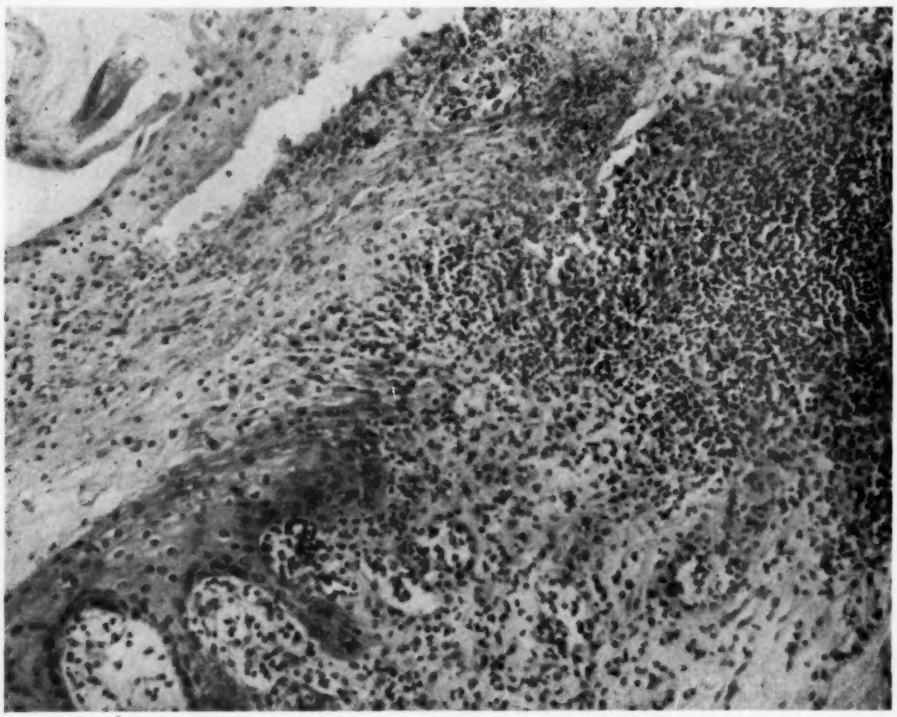


Fig. 1A.—Biopsy specimen from necrotic infected ulcer. Low power (×260). Note marked inflammatory reaction. Section taken before treatment.

From these studies we have now developed a more or less routine method of using sulfanilamide to prevent infections in contaminated open injuries and to control bacterial growth in grossly infected wounds. The first step is the proper preparation of the wound. In order for the drug to be effective it must come into direct contact with the invading organisms. The wounds must be adequately drained, necrotic tissue must be removed, and all surfaces of the wound made available for topical application of the powder. (Fig. 2 *A-C*.) When the field is thus prepared, a sufficient quantity of the concentrated sulfanilamide powder

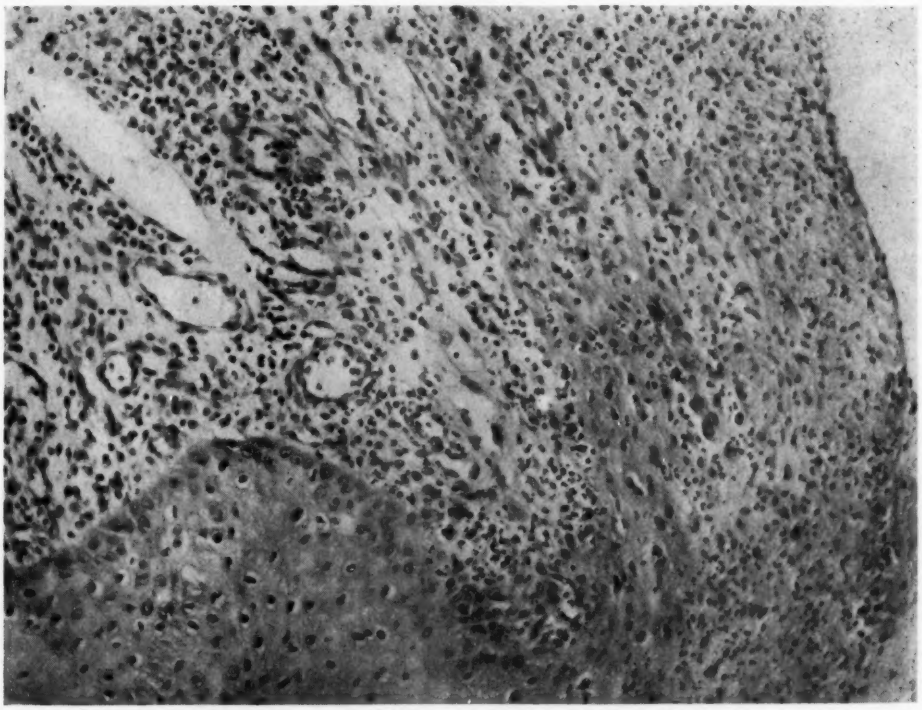


Fig. 1*B*.—Biopsy specimen taken from case shown in Fig. 1*A* after ten days' treatment with sulfanilamide locally. Low power (×260). There is a diminution in inflammatory reaction, but scant vascularization.

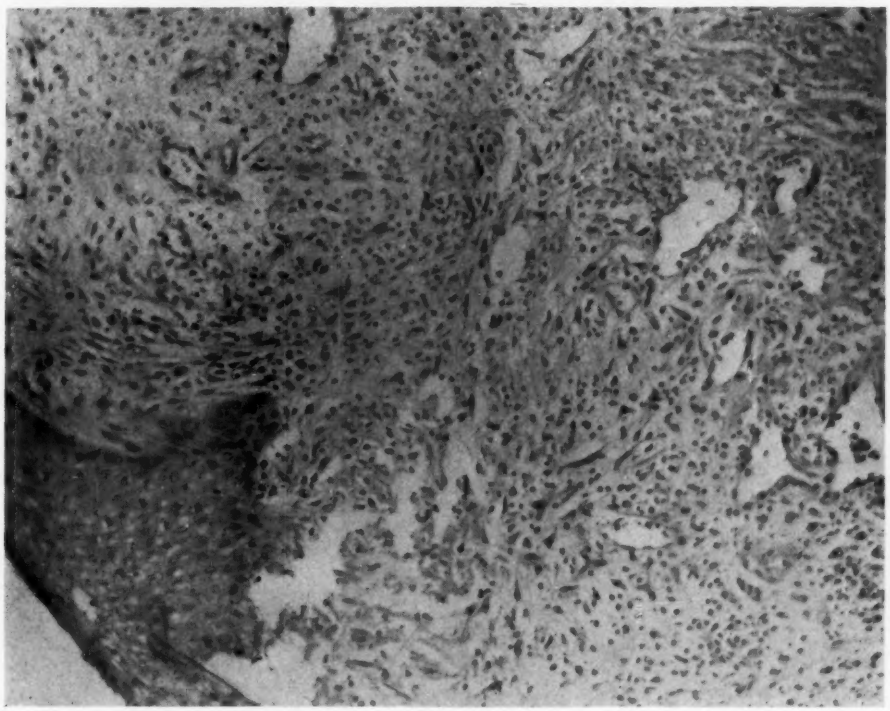


Fig. 1*C*.—Biopsy specimen of case shown in Figs. 1*A* and *B* ten days later after substituting sulfanilamide-allantoin ointment. Low power (×260). Note control of infection and abundant vascularization.

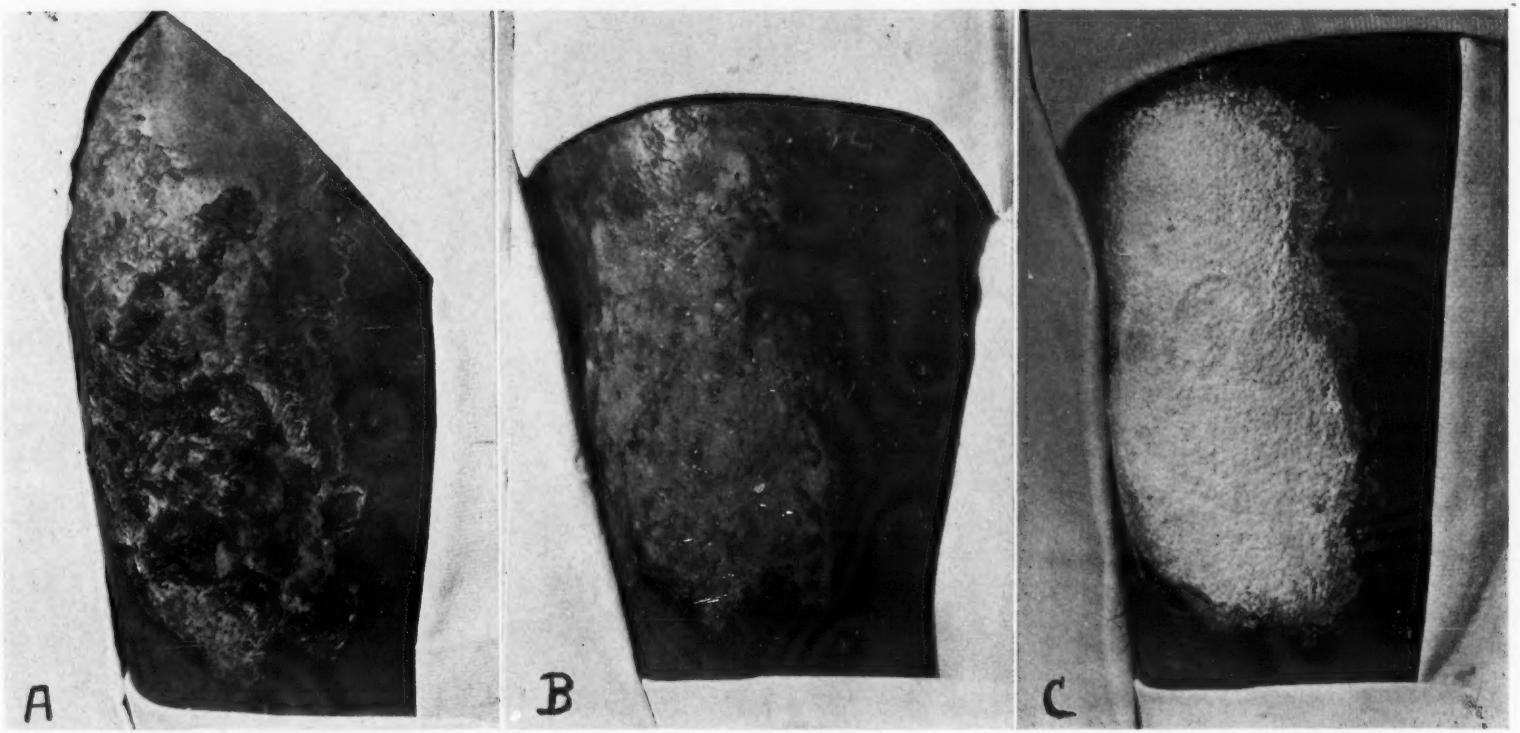


Fig. 2.—*A*. Photograph of infected burn of thigh showing crusting with exudate. *B*. Same case after débridement and control of bleeding. The field is thus made ready for the reception of the sulfanilamide powder. *C*. Same case showing entire lesion covered with sulfanilamide powder.

is placed upon the wound to cover the surface entirely and a dry dressing is applied. (We have not found it necessary to measure the dosage. In most cases 5 to 10 Gm. has been applied daily until the infection was controlled.) As soon as bacterial growth and exudate has diminished and the signs of inflammation have subsided, the powdered sulfanilamide is discontinued and is replaced by daily dressings of the sulfanilamide-allantoin ointment. The ointment is applied as a thin layer over the entire lesion, which is then covered with a dry gauze dressing. This type of treatment is continued daily until the wound is healed or until the field is covered with a skin graft.

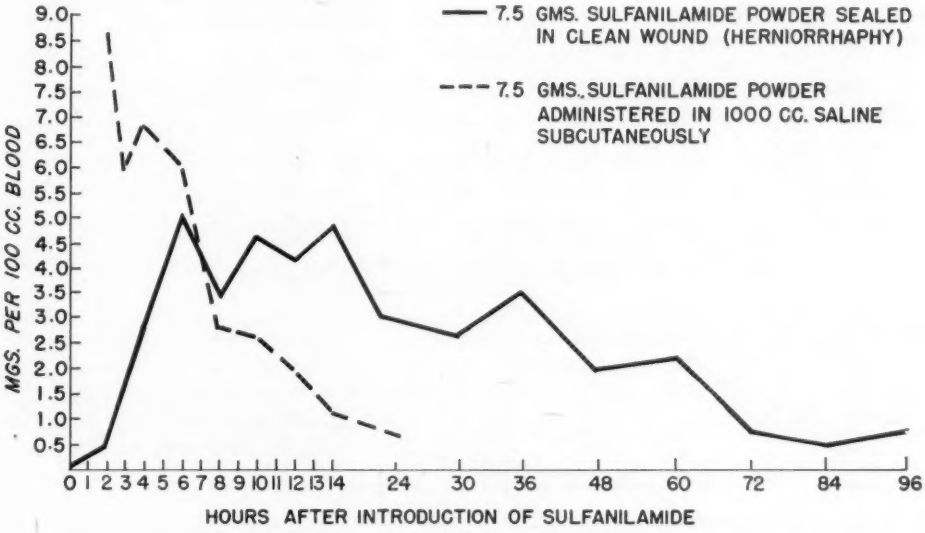


Fig. 3.—Chart showing comparison of blood sulfanilamide levels when 7.5 Gm. of sulfanilamide powder is sealed in a clean wound and the same dose given subcutaneously in 1,000 c.c. of normal saline solution. Note the delayed absorption of the drug from the sealed wound.

The method of treating infected wounds as outlined above has now largely replaced all other methods in our wards and in our out-patient clinics. The simplicity of the method is of great practical value. The disadvantages of wet dressings and irrigation techniques are overcome. Special mention should be made of its merits in preparing wide areas for skin grafts. Our percentage of graft "takes" has been greatly increased and the period of preparation has been materially reduced.

We have not attempted to measure the total dosage of sulfanilamide used in any particular wound. In many cases 5 to 10 Gm. of the powder was used daily for many days without any systemic symptoms. The blood concentration of the drug has been far less than that generally accepted as a "therapeutic level" for oral or parenteral administration in systemic diseases. In studying the rate of absorption from various types and sizes of wounds, we have found wide variations in the blood levels.

A single dose of 7.5 Gm. closed in a clean operative wound usually shows a rapid rise, approaching the level obtained by giving the same dose by mouth. There is then a gradual decline in the rate of absorption, but traces of the drug may be found in the blood for several days. (Fig. 3.) The same dose instilled in an open wound shows a much lower blood concentration (Fig. 4). In none of our cases has there been any evidence of a systemic toxic reaction. The peculiar cyanosis so frequently seen

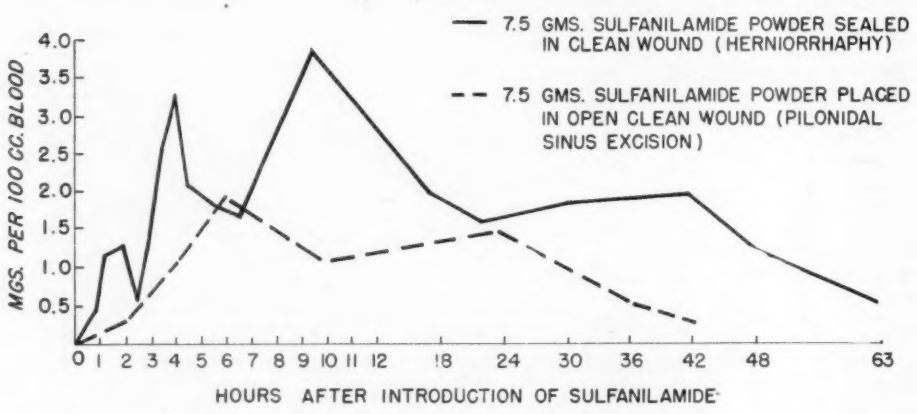

7.5 GMS. SULFANILAMIDE POWDER SEALED IN CLEAN WOUND (HERNIORRHAPHY)
7.5 GMS. SULFANILAMIDE POWDER PLACED IN OPEN CLEAN WOUND (PILONIDAL SINUS EXCISION)
MGS. PER 100 CC. BLOOD
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0 1 2 3 4 5 6 7 8 9 10 11 12 18 24 30 36 42 48 63
HOURS AFTER INTRODUCTION OF SULFANILAMIDE

Fig. 4.—Chart showing comparison of blood sulfanilamide levels from 7.5 Gm. of sulfanilamide powder when sealed in clean wound and when implanted in open wound.

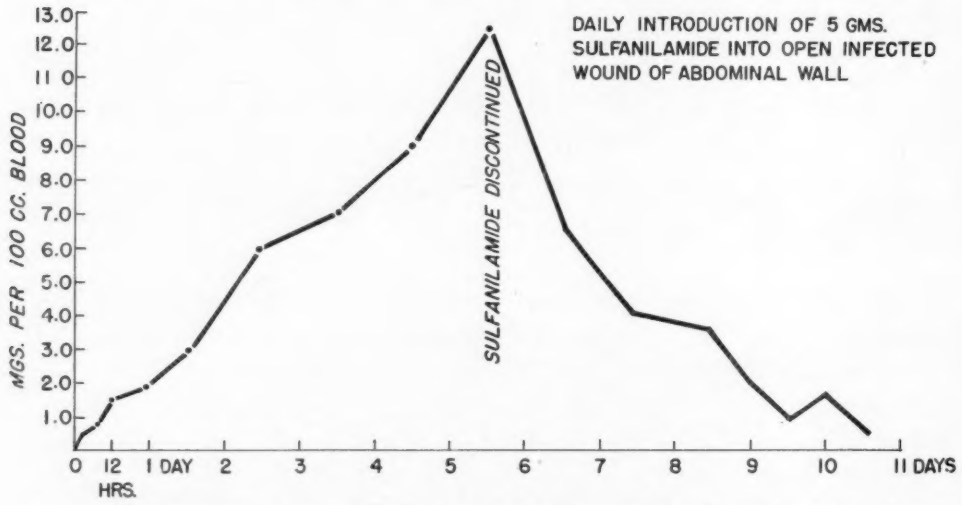


Fig. 5.—Chart showing accumulative rises of sulfanilamide blood concentration when 5 Gm. of the drug is applied daily in open infected wound.

when the drug is given by mouth or parenterally has not been observed in the locally treated cases. We have, however, observed a cumulative rise of the blood sulfanilamide level in certain cases in which large daily doses were used over a long period of time (Fig. 5). A recent article by Hooker and Lam[34] indicates that there may be a very rapid absorption from the extensive surfaces of acute burns. This possibility should be

borne in mind when using the concentrated powder over a prolonged course of treatment.

SUMMARY

Sulfanilamide powder rapidly controls bacterial growth in infected surgical wounds when it is placed directly into the lesion. The wound must be prepared by adequate drainage or débridement for the reception of the drug. The local action of sulfanilamide on the bacteria depends upon its molecular concentration in the wound. Therefore, it must be applied in sufficient quantity and must come into direct contact with the invading organisms. The growth of all the pyogenic organisms commonly found in infected wounds is apparently inhibited by sulfanilamide. Chief among these are streptococci, staphylococci, and the colon group. The common secondary invader, *B. pyocyaneus,* is promptly destroyed by local application of the drug. Prolonged use of concentrated sulfanilamide may retard healing. This probably results from inhibition of cellular growth and the retardation of vascularization of the granulation tissue. The substitution of sulfanilamide-allantoin ointment for the pure powder allows a prompt resumption of the normal healing process and at the same time maintains a clean wound.

REFERENCES

1. Meleney, F. L., and Harvey, H. D.: Combined Use of Zinc Peroxide and Sulfanilamide in the Treatment of Chronic Undermining Burrowing Ulcers, Ann. Surg. **110**: 1067, 1939.
2. Bricker, E. M., and Graham, E. A.: Inhibitory Effects of Sulfanilamide on Wound Healing, J. A. M. A. **112**: 2593, 1939.
3. Taffell, Max, and Harvey, S. C.: Effect of Sulfanilamide on Wound Healing, Proc. Soc. Exper. Biol. & Med. **45**: 647, 1940.
4. Key, J. A., and Burford, T. H.: The Local Implantation of Sulfanilamide in Compound Fractures; Its Effect on Healing, South. M. J. **33**: 449, 1940.
5. Key, J. A., Frankel, C. J., and Burford, T. H.: The Local Use of Sulfanilamide in Various Tissues, J. Bone & Joint Surg. **22**: 952, 1940.
6. Jensen, N. K., Johnsrud, L. W., and Nelson, M. C.: The Local Implantation of Sulfanilamide in Compound Fractures, SURGERY **6**: 1, 1940.
7. Campbell, W. C., and Smith, Hugh: Sulfanilamide and Internal Fixation in the Treatment of Compound Fractures, J. Bone & Joint Surg. **22**: 959, 1940.
8. Fields, R. J., and Weinstein, J. J.: The Use of Sulfanilamide Locally in the Treatment of Chancroid, Urol. & Cutan. Rev. **42**: 880, 1938.
9. Bonnin, N. J., and Fenner, F.: Local Implantation of Sulfanilamide for Prevention and Treatment of Gas Gangrene in Heavily Contaminated Wounds, M. J. Australia **1**: 134, 1941.
10. Buttle, G. A. H.: Chemotherapy of Infected Wounds, Lancet **1**: 890, 1940.
11. Dey, A. C.: Topical Application of Sulfanilamides, Indian M. Gaz. **75**: 161, 1940.
12. Levaditi, C., Gérard-Moissonier, Mme., Bréchot, H., and Tourney, R.: Sulfanilamide and Sulfanilamide Derivatives in Therapy of War Wounds Contaminated by Streptococci, Bull. Acad. de méd., Paris **123**: 39, 1940.
13. Rosenthal, L.: Action of Sulfanilamide in Vitro on Aerobic Sporogenic Bacilli, Proc. Soc. Exper. Biol. & Med. **43**: 78, 1940.
14. Long, Perrin H., and Bliss, E. A.: Bacteriostatic Effects of Sulfathiazole Upon Various Micro-organisms, Proc. Soc. Exper. Biol. & Med. **43**: 324, 1940.
15. Rake, G., and McKee, C. M.: Action of Sulfathiazol and Sulfamethylthiazol on Staphylococcus Aureus, Proc. Soc. Exper. Biol. & Med. **43**: 324, 1940.
16. Herrell, W. E., and Brown, A. E.: Local Use of Sulfamido Compounds in the Treatment of Infected Wounds, Proc. Staff Meet., Mayo Clin. **15**: 611, 1940.

17. White, H. J.: The Relationship Between Temperature and the Streptococcidal Activity of Sulfanilamide and Sulfapyridine in Vitro, J. Bact. **38**: 549, 1939.
18. Lawrence, C. A.: Bacteriostatic Actions of Three Thiazol Derivatives Upon Bacteria in Broth Cultures, Proc. Soc. Exper. Biol. & Med. **43**: 92, 1940.
19. Lawrence, C. A.: Bacteriostatic Effects of Sulfanilamide and Its Pyridine and Thiazole Derivatives Upon the Colon-Typhoid-Dysentery Group, Proc. Soc. Exper. Biol. & Med. **44**: 162, 1940.
20. Fox, C. L., Jr.: Is Sulfanilamide Bacteriostatic Under Anaerobic Conditions? Science **91**: 477, 1940.
21. MacLeod, C. M.: Inhibition of Bacteriostatic Action of Sulfanilamide by Substances of Animal and Bacterial Origin, J. Exper. Med. **72**: 217, 1940.
22. Schneider, L.: .Local Use of Sulfanilamide Powder and Hydrogen Peroxide in Wound Infections, Am. J. M. Sc. **201**: 208, 1941.
23. Lockwood, J. S.: Sulfonamide Therapy as an Aid to Surgery, Surg., Gynec. & Obst. **72**: 307, 1941.
24. Lockwood, J. S., and Lynch, H. M.: Mechanism of Action of Sulfanilamide; Influence of Proteolytic Products on Effectiveness, J. A. M. A. **114**: 935, 1940.
25. Main, E. R., Shinn, L. E., and Mellon, R. R.: Anticatalase Activity of Sulfanilamide and Related Compounds; Bacteriostatic Activity, Proc. Soc. Exper. Biol. & Med. **43**: 593, 1940.
26. Mellon, R. R., Locke, A. P., and Shinn, L. E.: Anti-enzymatic Nature of Sulfanilamide's Bacteriostatic Action, Am. J. M. Sc. **199**: 749, 1940.
27. Ravdin, I. S., Lockwood, J. S., and Rhoades, J. E.: The Use of Sulfanilamide in the Treatment of Peritonitis of Appendiceal Origin, Pennsylvania M. J. **43**: 1100, 1940.
28. Thompson, J. E., Brabson, J. A., and Walker, J. M.: The Intra-abdominal Application of Sulfanilamide in Acute Appendicitis, Surg., Gynec. & Obst. **72**: 722, 1941.
29. Veal, J. R., and Klepser, R. G.: Treatment of Pyogenically Infected Wounds by the Topical Application of Powdered Sulfanilamide and Sulfanilamide-Allantoin Ointment, M. Ann. District of Columbia **10**: 61, 1941.
30. Mayo, C. W., and Miller, J. M.: Solution of Sulfanilamide in the Local Treatment of Wounds, Proc. Staff Meet., Mayo Clin. **15**: 609, 1940.
31. Robinson, Wm.: Stimulation of Healing in Nonhealing Wounds by Allantoin Occurring in Maggot Secretions and of Wide Biological Distribution, J. Bone & Joint Surg. **17**: 267, 1935.
32. Shipp, M. E., and Hetherington, D. C.: Effect of Allantoin Upon Growth of Fibroblasts From Cardiac Explants in Tissue Culture, Proc. Soc. Exper. Biol. & Med. **35**: 180, 1936.
33. Greenbaum, F. R.: Allantoin, a New Granulation Tissue Stimulating Substance With Special Emphasis on Allantoin in Ointment Form, Am. J. Surg. **34**(n.s.): 259, 1937.
34. Hooker, Donald H., and Lam, C. R.: Absorption of Sulfanilamide From Burned Surfaces, SURGERY **9**: 534, 1941.

CHANGES PRODUCED BY SYMPATHECTOMY IN THE ELECTRICAL RESISTANCE OF THE SKIN

CURT P. RICHTER, PH.D., AND BETTYE G. WOODRUFF, BALTIMORE, MD.

(From the Psychobiological Laboratory, Phipps Psychiatric Clinic, Johns Hopkins Hospital)

SURGICAL treatment of circulatory disturbances of the skin has been handicapped (a) by a lack of knowledge regarding the distribution of the sympathetic nerves to the skin and (b) by the lack of an adequate method of demonstrating the skin areas affected by sympathectomy. These shortcomings have been overcome, at least in large part, by the use of the so-called electrical skin resistance method.

This method depends on the changes produced by sympathectomy on the resistance offered by the skin to the passage of a small direct electrical current. Since various factors influence skin resistance, a brief review will be given at this point of some of the essential underlying neurologic and physiologic principles, as well as of the origin of our interest in problems concerned with the electrical resistance of the skin.

Incidental to early studies on the galvanic skin reflex in psychiatric patients, it was found that some patients had a very high skin resistance which reached levels of 1,000,000 to 3,000,000 ohms, while others had a resistance of only a few thousand ohms. A separate investigation was then undertaken to determine whether these resistance levels could be correlated with the different types of psychoses and at the same time to learn more about the physiologic and neurologic factors underlying the resistance offered by the body to the passage of a small direct current.

For these experiments the following technique was used: Four solid disks of zinc were used as electrodes. These were placed against the palmar and dorsal surfaces of the two hands, using a paste made of kaolin and saturated zinc sulfate solution to provide a contact between the electrodes and the skin. Any pair of these electrodes could be connected to a galvanometer which measured the resistance offered to the passage of an imperceptible current.[1, 2]

From these studies the following information was obtained: (a) The resistance offered by the body to the passage of a small direct current is localized almost entirely in the skin. Punctures made through the skin underneath the electrodes reduced the resistance instantaneously from any level, however high, to only a few hundred ohms. Similarly, abrasions of the skin greatly reduce the resistance. (b) The resistance of the skin varies to a certain extent with its anatomical structure, chiefly with its supply of sweat glands. Thus, the porous areas of the palmar surfaces of the hands usually have a lower resistance than the skin on the relatively nonporous areas of the dorsal surfaces. Thus, for nine normal individuals the palmar resistance averaged 77,100 ohms; the dorsal

Received for publication, May 10, 1941.

resistance, 290,310 ohms.[3] (c) The resistance on both surfaces depends largely on the sweat gland activity, being high when the sweat glands are inactive (that is, when the skin is dry) and low when the sweat glands are active (that is, when the skin is moist). (d) The resistance readings on the porous and nonporous areas may vary independently of one another. (e) Skin resistance varies with normal and pathologic sleep and sleep induced by hypnotics, in general, being high during sleep and low during the waking state.[2, 4-6]

It also was found that skin resistance is controlled to a large extent through the autonomic nervous system. In our first experiments, applying to monkeys essentially the same technique used on human beings, it was found that section of the entire nervous supply to the extremities (in the upper extremities the brachial plexus, in the lower extremities the sciatic and femoral nerves) greatly increased the resistance, especially on the palmar surfaces of the hands and feet. In some animals the palmar resistance increased from 20,000 or 30,000 ohms to 5,000,000 or 10,000,000 ohms, at which levels it remained permanently. The section of these trunks included sympathetic and somatic nerves. Further experiments were undertaken to sever these two types of nerves separately. Section inside of the cord of all of the anterior and posterior roots to the foreleg, which removed all of the somatic supply but did not interfere with the sympathetic nerve supply, had no effect on the skin resistance. Removal of the sympathetic chain, however, produced as great an initial increase in skin resistance as section of the entire nerve. After several months the resistance decreased to a permanent level of 1,000,000 to 2,000,000 ohms, which was still far above the preoperative level. It was thus proved that skin resistance depends primarily on the sympathetic nervous system.[2, 7]

This same technique has been used to study injury and repair within the sympathetic nervous system.[8-10] In experiments on cats it was found that a preganglionic section of the white rami to the stellate and first thoracic ganglion produced a large but temporary increase in skin resistance on the central pads of the forefeet. The resistance, which returned to its preoperative level in twenty to sixty days, closely paralleled the return of normal sweat gland activity. Thus, skin resistance gave a good measurement of the regeneration of the preganglionic fibers. Postganglionic sympathectomy through section of the gray rami from the stellate ganglion and the first thoracic ganglion produced an even greater increase in skin resistance on the larger central pads, but the resistance did not return to its preganglionic level. Even after ten months the resistance in some of the cats averaged over 3,000,000 ohms. The considerably higher levels of skin resistance produced by postganglionic as compared to preganglionic sympathectomy demonstrated that the ganglia have at least a certain degree of independent control over the peripheral mechanisms. This independence of function of the sympathetic ganglia may be the basis of the difference in the responses

of the vascular system to adrenalin after preganglionectomy and postganglionectomy reported by White and co-workers,[11-13] Grant,[14] and Ascroft.[15]

The dependence of skin resistance on the sympathetic nervous system was further brought out by experiments made on cats and monkeys in which the spinal cord was sectioned at various levels, above and below the thoracolumbar outflow of the sympathetic nerves. Complete transections made at C_7 and C_8 (that is, above the thoracic outflow) produced a large increase in the palmar resistance on both the fore- and hindfeet; complete transection at T_7 (that is, below the thoracic outflow to the foreleg) had no effect on the forefeet but produced a large increase in the resistance of the hindfeet; complete transection at L_3 (that is, below the outflow to both fore- and hindfeet) which completely paralyzes the hindlegs, had no effect on the skin resistance of either the fore- or hindfeet.[16] Further, the resistance closely followed the condition of the spinal cord. During the period of shock, when the legs were completely paralyzed, the resistance remained high; gradually, as the spinal reflexes began to appear, the resistance decreased. However, the return of the spinal reflexes preceded by many days the return of the normal function of the sweat glands, as shown by the return of the skin resistance to its preoperative level.

This method was applied in 1927 to the study of a patient in whom a tumor had completely blocked off the sympathetic chain on the right side of the neck and all of the sympathetic connections to the right arm and hand. In this patient the resistance of the palmar and dorsal surfaces was considerably higher on the side of the lesion. In the sweat bath the right hand remained dry.[17] In 1937 observations were made on the palmar and dorsal resistance changes of the hands of eight patients with cervical sympathectomies and of two patients with lumbar sympathectomies. They all showed respectively a greatly increased resistance on the palmar and dorsal surfaces of the hands and on the plantar and dorsal surfaces of the feet.[18] Smithwick[19] has recently reported that sympathectomy increases skin resistance.

METHODS

The method which has now been devised makes it possible to determine changes produced by sympathectomy on the electrical resistance of the skin not only on the palmar and dorsal surfaces of the hands but also on all other parts of the body (see Fig. 1). A zinc sheet disk, ½ inch in diameter, was attached to the lobe of one ear with an earring clip directly over a skin puncture made with a hypodermic needle. A paste made of kaolin and saturated zinc sulfate solution made contact between the electrode and the skin. The puncture through the skin reduced the resistance under this electrode to a negligibly low level. The other electrode consisted of a zinc sheet, about ¼ inch in diameter, attached at right angles to an insulated handle, about 3 inches long. By the

handle this electrode could be held against the skin and could be moved freely from place to place. The use of this electrode represents one of the most important steps in this technique. In our former studies electrodes were fixed firmly to only four surfaces, the palms and backs of the two hands, and further contact between the electrodes and the skin was made with the kaolin paste. We had always thought that the paste was necessary in order to eliminate polarization. With this electrode no paste is used; the polished surface of the zinc is applied directly to the skin. Thus, it became possible to explore the skin without covering the body with kaolin paste. Furthermore, this electrode eliminates a drop in skin resistance produced in some instances by stimulation from the kaolin paste.

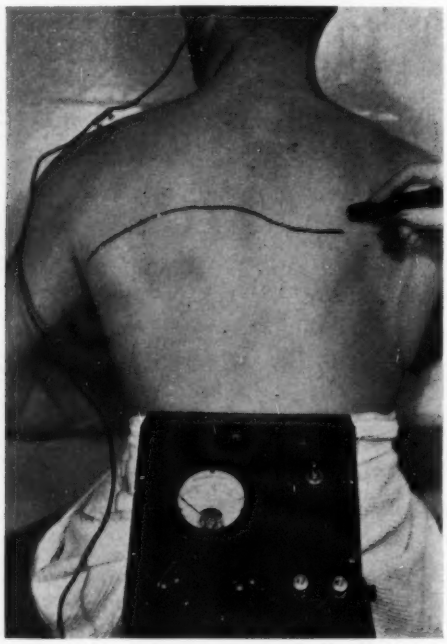


Fig. 1.

The electrodes were connected to a dermometer or an ammeter. The dermometer, described in detail by Levine,[20] had been used for most of our previous studies on skin resistance. It has two dials, one to show the amperage of the current flowing through the circuit, the other the resistance offered to the current.

A simple and less expensive instrument for this purpose was built for us by Mr. Frederick Whelan, of the Department of Electrical Engineering of the Johns Hopkins University. It contained an ammeter, a nine-volt battery, and a rheostat to adjust the voltage. Fig. 1 shows this instrument.

For the examination we used the following procedure. The patient was heated in a hot-air cabinet for a few minutes. After this the movable hand electrode was held gently against the skin on any part of the body and the voltage adjusted so that a small current flowed through the

circuit. Then the electrode was moved quickly from place to place over the surface of the body in jumps of approximately 6 inches. When a sudden change in the flow of the current was found, that is, either an increased or a decreased flow, the region was further explored until the line of demarcation between the areas of high and low resistance was located. This point was marked with a soft skin pencil (black for white patients and white for colored patients). Often the change from high to low resistance occurred within a few millimeters. When a second point of demarcation was determined, a line was drawn through the two points. The process was repeated at a distance of several inches at either end of the line until finally the entire areas of high and low resistance were defined.

An attempt was made to keep the current below the range in which it could be felt by the patients. The sudden fall in resistance from millions of ohms to only a few thousand ohms made it difficult always to make certain that the current remained imperceptible. The first tingling sensation reported by the patient usually came simultaneously with the drop in resistance.

The present report contains records made on 20 patients operated upon at Johns Hopkins Hospital and at the Baltimore City Hospital at Bayview and at two other hospitals in other cities. Five of the patients had upper thoracic and 15 had lumbar sympathectomies. Six patients had Raynaud's disease, 3 Buerger's disease, 3 arteriosclerosis, 3 hypertension, 2 chronic leg ulcer, 1 acrocyanosis, and 1 postphlebitic edema. The upper thoracic sympathectomy closely conformed to the operation used by Smithwick.[21] The white and gray rami from the second and third ganglia were sectioned, about 1 inch of the anterior and posterior roots of the second and third intercostal nerves removed, and the chain below the third ganglion sectioned. The third ganglion was brought out through the incision and sutured to a muscle in order to prevent regeneration. Since the ganglia which carry the sympathetic nerves to the arms remained in connection with the extremities, this represents a preganglionic type of sympathectomy. The lumbar sympathectomies also were usually of the preganglionic type, including the removal of the ganglia either at L_1 and L_2, or at L_1, L_2, and L_3, or at L_2 and L_3. However, in some patients the operation was at least partially of the postganglionic type, including the removal of the ganglia at L_4 or at L_4 and L_5. In one patient operated upon in another hospital the removal must have included only the ganglia at L_4 and L_5.

Records were taken at ordinary room temperature immediately after the patients had been heated for a few minutes in a hot-air cabinet.

The relation of the areas of high resistance to areas which do not sweat was determined by means of the Minor starch sweating test.[22] The skin was painted with a mixture of castor oil and iodine. After this mixture had been allowed to dry, an even layer of rice starch powder was dusted over the skin. Then the patient was heated in a hot-air

cabinet until active sweating started. The moisture from the sweat dissolves the starch and turns the mixture black. Areas which do not sweat remain white. The sweating test was made immediately after the completion of the skin resistance test and while the lines of demarcation were still on the skin. The two areas were superimposed upon one another, and thus we could compare them accurately.

A. *B.* *C.*

Fig. 2.

RESULTS

The photographs in Fig. 2 show the patterns obtained from three patients with dorsal sympathectomies. The first patient, a man 38 years of age (Fig. 2*A*), had had a left dorsal sympathectomy for Raynaud's disease four months previously. The photograph at the top shows the area of high resistance, which included the left half of the face and neck and the chest just above the nipple, part of the axilla and the under surface of the arm, and a small area on the back about five inches below the level of the shoulders. The photograph at the bottom shows the results of the Minor sweating test. The black areas show active sweating; the white areas, no sweat. The high skin resistance areas and the areas which did not sweat show an almost exact cor-

respondence, except for an area on the right side of the mouth which did not sweat. This area often does not sweat in normal individuals.

Fig. 2*B* gives the photographs of a young woman with a bilateral dorsal sympathectomy. The area of high resistance included her head, neck, and chest below the breasts, the axillae, and a line across her back at the same level. The Minor test again showed a close correspondence between areas of sweat gland activity and high skin resistance, except for

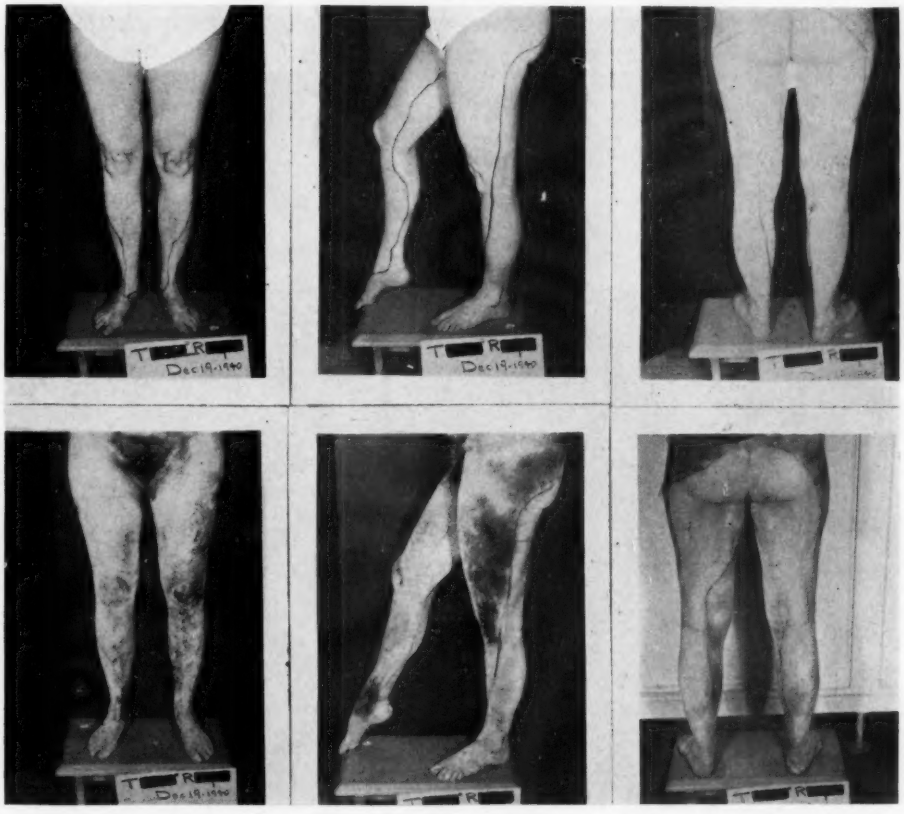


Fig. 3.

the skin on the breasts which showed many punctate areas of sweat up to a line at the anterior level of the breasts. At this line the skin resistance dropped to a lower level than in the main large areas, but not down to the level of the resistance of the skin on the rest of the body. Such areas of partial decrease in skin resistance, which must indicate that some sympathetic innervation still remained and which we have found in other patients, we call "zone" areas. These areas must result from overlapping of the distribution of the adjacent dermatomes.

Fig. 2*C* gives the photographs of a man on whom a bilateral dorsal sympathectomy had been performed eight months before for Raynaud's disease. The area of high resistance was similar to those found in the other two patients, except for a small "zone" area on the face. In the

Minor sweating test this area contained several patches of black spots. It is possible that this area received some fibers from the first thoracic nerve.

These patterns of skin resistance and sweating closely agree with those which have been described by List and Peet[23] and others who used only the Minor test.

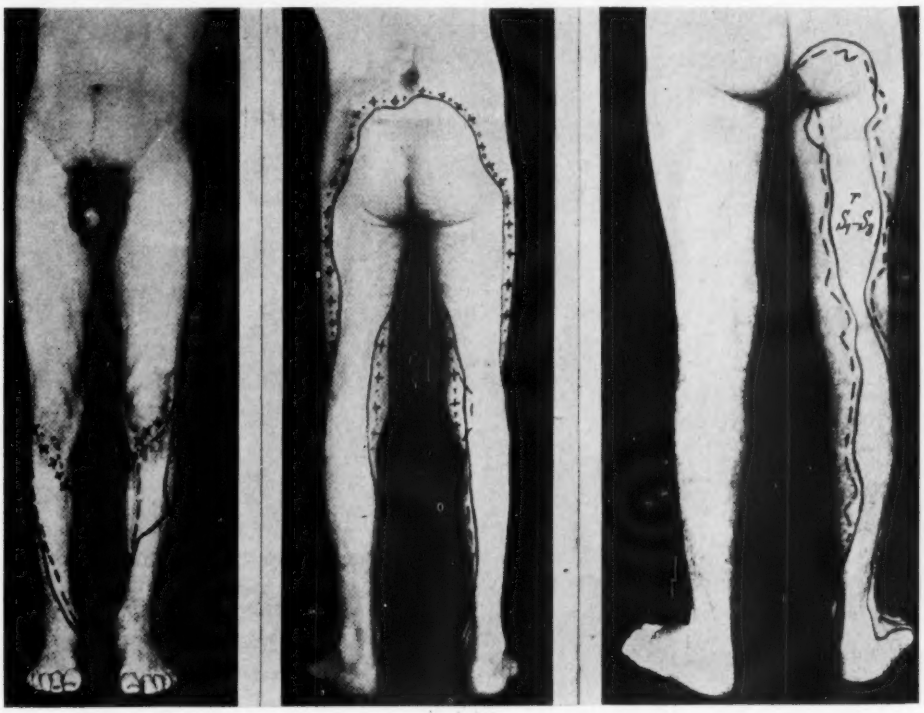
Lumbar sympathectomy produced high skin resistance areas with patterns which hitherto had not been described. Fig. 3 shows three views of the same patient with the skin resistance pattern and with the skin

A. *B.* *C.*

Fig. 4.

resistance and sweating test patterns superimposed. The surgeon's notes stated that either L_2, L_3, and L_4 or L_3, L_4, and L_5 had been removed. The areas which again showed a close correspondence between skin resistance and sweating included the skin over the buttocks, down the posterior surface of the legs in a fairly narrow strip to the ankles, and over the backs and soles of the feet. In the 4 other patients who showed this pattern the surgeons stated that they had removed three ganglia below either L_2 or L_3. A slightly different pattern is shown in Fig. 4*A*. The area of high resistance included the anterior as well as the posterior surfaces of the calves of the legs up to a line which fell

just below the kneecap. In the 5 other patients who showed this pattern the surgeons reported that 2 or 3 ganglia below L_1 or L_2 had been removed. Still another pattern is shown in Fig. 4*B*. In this case the area of high resistance included all of the posterior surface of the thigh and part of the anterior surface on the inside and above the knee. Two patients showed this pattern; in both the operation included the ganglia at L_2, L_3, and L_4. The last pattern is shown in Fig. 4*C*. In this patient the area of high resistance included the entire surface of the leg in the front up to the groin and in the back up to the buttock. In this patient three ganglia below T_{12} had been removed. This is the only patient that showed this pattern.



A. *B.* *C.*

Fig. 5.

At the beginning of this study, when we had taken records on only a few patients, these different patterns did not seem to follow any special plan. We were most perplexed by the narrow area of high resistance which ran from the ankles up to the buttocks. The dermatome chart of the distribution of sensory nerves worked out by Head did not show any such well-defined areas, and Peet in his studies on sympathectomized patients with the Minor test had not found any pattern below the curved line across the upper border of the buttocks. Later, however, after we had taken records on more patients and had found with great consistency the same patterns, also after we had found that patients with lesions of sensory nerves below L_4 showed anesthesia over a strip along

the posterior surface of the leg, we concluded that these areas of high resistance closely follow the distribution of the sensory nerves and that the pattern varied with the level of the ganglionectomy. Figs. 5*A* and 5*B* show the areas of anesthesia mapped out by Foerster[24] on a patient with a traumatic transection of the cauda equina immediately below the outflow of the third lumbar nerve. It will be noted that these areas are almost identical with those shown in Fig. 3. Fig. 5*C* also taken from Foerster shows an even narrower strip area along the posterior surface of the leg in a patient with a resection of S_1, S_2, and S_3. This area is almost identical with that on the left leg in Fig. 7*B*.

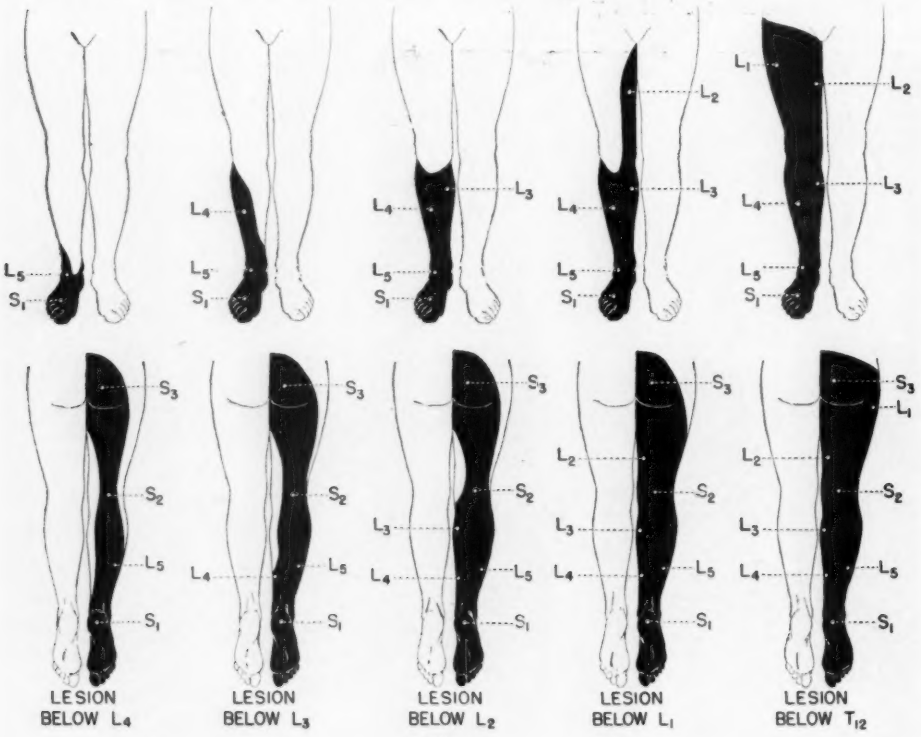
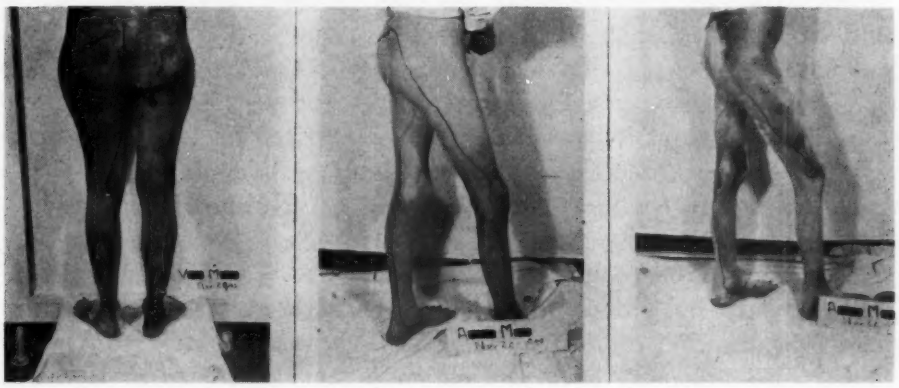


Fig. 6.

Fig. 6 gives a schematic representation of the different patterns arranged according to the level of the ganglionectomy beginning with a section below L_4 and ending with a section below T_{12}. The overlapping areas of the distribution of the sensory areas were taken from the distribution charts of Head[25] and of Foerster.[24] The latter was published by Fulton.[26] In these figures the arrows point not to the center of the sensory areas but to the lowest part of the area which overlaps with the adjacent dermatomes. When L_4 was the last intact ganglion, the area of high resistance included L_5, S_1, S_2, and S_3. Each successively higher ganglionectomy included more of the surface of the leg until finally it included the entire surface. Of the 15 patients, 1 showed the first pattern, 5 the second, 6 the third, 2 the fourth, and 1 the fifth; one with an unsuccessful operation showed no increased resistance at all. In nearly

every instance the location of the lesion worked out from the sensory distribution chart of the different patterns coincides with the level at which the operator stated that the lesion had been made, with the exception that in two patients in whom the surgeons stated that the first lumbar ganglion had been removed the area of high resistance did not include all of the anterior surface of the thigh. The discrepancies which existed may have been due to the variations in the location and fusion of the ganglia, as well as to the difficulties of identifying the different ganglia during the operation.

On the basis of this knowledge of the close correspondence between the sympathectomy and sensory dermatomes found for the various lumbar sympathectomies, it is possible now to state that the same principle applies also to the dorsal sympathectomies. According to the dermatome chart of Foerster, the overlap of the fourth dorsal dermatome should extend approximately 1½ to 2 inches above the level of the nipples. In the three patients described above in whom the lesion was made below the third lumbar ganglion, the lower border of the affected area was approximately 2 inches above the level of the nipples.



A. *B.* *C.*

Fig. 7.

Thus far we have used this method chiefly to determine within a few days postoperatively the results produced by sympathectomy performed at the Johns Hopkins Hospital and at the Baltimore City Hospital. We have also used the test to determine whether or not regeneration had taken place in patients operated upon two to three years previously and on patients operated upon in other hospitals in whom the success of the operation was doubtful. Fig. 7*A* shows the mapping of the high resistance areas in a patient who had had a bilateral lumbar sympathectomy two years before. On one side she showed the typical areas. On the other the skin showed the same level of resistance over its entire surface. The results of the Minor test confirmed this finding. This would indicate either that originally the chain on the left side had not been removed or that regeneration had taken place. Since the operation was successful on one side, it would seem likely that the removal had

been incomplete on the other side, thus allowing regeneration. Clinically symptoms of hypertension were again present in this patient.

We used the test for the examination of a patient brought to Johns Hopkins Hospital from another hospital. The patient suffered from Raynaud's disease. He stated that four months before he had had an abdominal nerve operation in another hospital for this condition. Clinically it was difficult to determine whether he had actually been sympathectomized. Our test showed no areas of high resistance on either leg. The Minor test showed an even distribution of sweating on both legs. It was concluded that the sympathetic chain must still be intact on both sides.

The same method was used in another patient who likewise had been sent here from another hospital. He showed severe Raynaud-like symptoms, which were, however, not entirely typical, in his feet, hands, nose, and ears. The report from the other hospital stated that a bilateral lumbar sympathectomy had been performed more than six months before. Clinically it was not clear that the sympathectomy had been performed. Some of the clinicians who saw the patient stated that he sweated; others, that he did not. A dorsal sympathectomy for his nose and ears was considered. However, the clinicians did not want to recommend this operation if a lumbar sympathectomy had been performed without any visible improvement. Skin resistance tests showed that lumbar sympathectomy had been performed on both legs, probably below L_2 on one leg and below L_5 on the other leg. The photographs in Figs. 7*B* and 7*C* show the areas. The Minor test completely confirmed our findings.

We have also had occasion to use this method for the examination of areas affected by ganglionic alcohol block. Here also, it gives a very sharp demarcation of the affected areas. Similarly, in three cases of spinal cord lesion we have also obtained sharply defined areas which corresponded to the location of the lesion in the cord.

DISCUSSION

Up to the present the Minor starch sweating test was the only available method for the determination of areas of skin on the head and on the body which had been affected by sympathectomy. This method has several shortcomings. It requires a considerable amount of time and skill to paint evenly the entire body, or only half the body, with the castor oil and iodine mixture and to cover it with the starch powder. Furthermore, after the test a shower and scrubbing are required to remove the mixture. On colored patients the results often cannot be interpreted; further, since many individuals do not sweat even when placed in the hot-air bath, its use is limited. The lines of demarcation between areas that sweat and those that do not are not always sharply defined. The failure of Peet to discover the pattern on the legs which we have found with the skin resistance method shows the shortcomings

of the starch method. However, once the presence of these areas was definitely known, special care in giving the Minor test also brought out the same pattern of sweating.

In contrast, the skin resistance method requires very little time. The mapping for cervical and lumbar sympathectomies requires only five to ten minutes. The lines of demarcation are sharp and remain quite constant from day to day. Only a small amount of external heat is necessary to bring out the difference in resistance in the different areas. The test can be made equally well on colored and white individuals and on individuals who do not sweat enough for application of the Minor test.

The results seem to establish a close correspondence between sensory and sympathetic dermatomes. The exact determination of the sympathetic dermatomes will have to wait for experimentation on monkeys or apes in which skin resistance mappings are made after removal of two or three ganglia. It is very likely that by means of the skin resistance method it will be possible to map out areas affected by removal of only one ganglion. The affected area would be expected to show itself as a "zone" area despite the overlapping of the two adjacent dermatomes.

These skin resistance tests show that the dorsal sympathectomy as performed by Telford,[27] Livingston,[28] and Smithwick[29] affects the head, neck, and all of the arm, except small areas under the armpit. It is fully adequate for sympathetic denervation of the upper extremities. The tests show that the removal of the second and third lumbar ganglia denervates all of the leg below the knee and all except the anterior surface of the thigh above the knee. This is in agreement with the conclusions arrived at by Smithwick[21] on the basis of clinical studies. Removal of the first lumbar ganglion, which denervates the entire leg, would probably be better, except for the fact that in men it interferes with ejaculation.

Since such a close correspondence exists between the areas of high resistance and the distribution of the sensory nerves, this test may be used in the mapping of areas of sensory loss; and it would have the additional advantage that it does not depend on cooperation on the part of the patient.

SUMMARY

1. A method was described by means of which areas affected by sympathectomy can be mapped on all parts of the body. These areas offer a high resistance to the passage of a very small direct current. The unaffected areas have the normally low resistance. The line of demarcation between the two areas usually is so sharp that the resistance may drop from many thousand ohms to only a few hundred ohms in less than ¼ inch.

2. The areas of high resistance do not sweat. This was demonstrated by the Minor starch sweating test. The areas of high resistance and of nonsweat gland activity showed an almost perfect correspondence.

3. Twenty patients were studied with this method, 3 with dorsal sympathectomy and 17 with lumbar sympathectomy.

4. The areas of high resistance produced by sympathectomy closely followed the sensory dermatomes. The lumbar sympathectomy brought out this relationship most clearly. Five different patterns produced by lesions below T_{12}, L_1, L_2, L_3, and L_4 were demonstrated.

5. The method was applied in determining the success of sympathectomy, the areas of skin affected by the operation, and the presence of regeneration.

6. Similarly, skin resistance tests were used in localizing spinal cord lesions.

7. Compared to the Minor starch sweating test, the determination of skin resistance is simple and involves less time and discomfort for the patient; it can be used on colored as well as on white patients and on individuals who do not sweat sufficiently to color the starch paste; and it gives very sharp boundary lines between affected and unaffected areas.

8. Since this technique requires little or no cooperation from the patient, it should be useful for the mapping of sensory dermatomes.

We want to thank Dr. H. B. Shumacker, Jr., and Dr. I. R. Trimble of the Department of Surgery and Dr. F. R. Ford of the Department of Neurology for their very helpful cooperation.

REFERENCES

1. Richter, C. P.: Am. J. Physiol. **68**: 147, 1924.
2. Richter, C. P.: Proc. Nat. Acad. Sc. **12**: 214-222, 1926.
3. Richter, C. P.: Arch. Neurol. & Psychiat. **19**: 488-508, 1928.
4. Richter, C. P.: Arch. Neurol. & Psychiat. **21**: 363-375, 1929.
5. Richter, C. P.: Am. J. Dis. Child. **40**: 18-26, 1930.
6. Richter, C. P.: J. Pharmacol. & Exper. Therap. **4**: 471-486, 1931.
7. Richter, C. P.: Bull. Johns Hopkins Hosp. **45**: 56-74, 1929.
8. Tower, S. S., and Richter, C. P.: Arch. Neurol. & Psychiat. **26**: 485-495, 1931.
9. Tower, S. S., and Richter, C. P.: Arch. Neurol. & Psychiat. **28**: 1139-1148, 1932.
10. Tower, S. S., and Richter, C. P.: Arch. Neurol. & Psychiat. **28**: 1149-1152, 1932.
11. White, J. C.: The Autonomic Nervous System, New York, 1935, The Macmillan Co.
12. White, J. C., Okelberry, A. M., and Whitelaw, G. P.: Arch. Neurol. & Psychiat. **36**: 1251-1276, 1936.
13. White, J. C.: New England J. Med. **216**: 91-94, 1937.
14. Grant, R. T.: Clin. Sc. **2**: 1-26, 1935.
15. Ascroft, P. B.: Brit. J. Surg. **24**: 787-815, 1937.
16. Richter, C. P., and Shaw, M. B.: Arch. Neurol. & Psychiat. **24**: 1107-1116, 1930.
17. Richter, C. P.: Brain **50**: 216, 1927.
18. Richter, C. P., and Levine, M.: Arch. Neurol. & Psychiat. **38**: 756-760, 1937.
19. Smithwick, R. H.: Arch. Surg. **40**: 286-306, 1940.
20. Levine, M.: Arch. Neurol. & Psychiat. **29**: 828-842, 1933.
21. Smithwick, R. H.: New England J. Med. **222**: 699-703, 1940.
22. Minor, V.: Deutsche Ztschr. f. Nervenk. **101**: 302-308, 1928.
23. List, C. F., and Peet, M. M.: Arch. Neurol. & Psychiat. **40**: 27-43, 1938.
24. Foerster, O.: Handbuch der Neurologie, Berlin, 1936, Julius Springer.
25. Head, H.: Studies in Neurology, London, 1920, Oxford University Press.
26. Fulton, J. F.: Physiology of the Nervous System, London, 1938, Oxford University Press.
27. Telford, E. D.: Brit. J. Surg. **23**: 448-450, 1935.
28. Livingston, W. K.: Clinical Aspects of Visceral Neurology, Springfield, 1935, Charles C Thomas, Publisher.
29. Smithwick, R. H.: Ann. Surg. **104**: 339-350, 1936.

NEPHROLITHIASIS DUE TO INFECTION WITH THE BACILLUS PROTEUS*

C. D. Creevy, M.D., Minneapolis, Minn.

(From the Urological Division of the Department of Surgery, the Medical School of the University of Minnesota)

BACILLUS PROTEUS

THE *Bacillus proteus* was first systematically investigated by Hauser in 1885. It is widely distributed in nature, having been found in soil, decomposing animal matter, and in human and animal feces. It is a pleomorphic, motile, gram-negative rod one to thirty microns in length, and rapidly forms a spreading "ground-glass" layer on solid media, in which it liquefies gelatin and produces indol, phenol, nitrites, hydrogen sulfide, and ammonia (Meyerhof). It is finally identified by its fermentation of certain sugars to acid and gas (Topley and Wilson). Inoculated into animals, it may die, produce abscesses, or cause septicemia. It is only weakly antigenic. In man it has caused infections in the middle ear, mastoid, meninges, intracranial sinuses, eye, nose, throat, gall bladder, peritoneum, female internal genitals, bones, testes, and urinary tract.

INFECTION OF URINARY TRACT

According to Cabot and Smith the *B. proteus* probably reaches the urinary tract only through instrumentation, although Chute has had 2 cases in which there was no such history.

Schulte did not find it in an investigation of the bacterial flora of the urinary tract, Streng having found it in such circumstances in but 3 of 33 cases. Important factors in localization are stasis, recumbency, and wasting diseases.

It is a common resident of the human bowel, Dr. M. Levine, bacteriologist at the University of Minnesota Hospitals, having found it on a single culture of the stool in 22 of 53 consecutive patients taken at random from the wards as well as in 4 of 6 bed sheets used by patients without clinical evidence of infection with *B. proteus*. Thus, it is clear that the organism may be present about the external urinary meatus and may be introduced by an urethral instrument, or may grow along the outer surface of an inlying catheter. Such a catheter, whether in the urethra, a suprapubic fistula, or in the kidney, may be contaminated either directly or from linen not grossly soiled.

The route by which the organism, having been introduced into the bladder, invades the kidneys, is not definitely known, but Scott found *B. proteus* in the blood in 5 of 82 patients with urethral chill, suggesting arrival by way of the blood stream. Theoretically, of course, it may

*Read before the New York Academy of Medicine on Dec. 18, 1940.
Received for publication, March 11, 1941.

ascend the periureteral lymphatics or the lumen of the previously diseased ureter or follow the lymphatics from the ascending colon to the right kidney. The latter route may account for infections in the absence of instrumentation.

According to the literature, *B. proteus* is not a very common invader of the urinary tract, having occurred in 135 (5.4 per cent) of 2,502 cases of urinary infection in five reported series (Cabot, Streng, Kretschmer and Mason, Scott, and Scott and Sandholzer).

MECHANISM OF FORMATION OF STONE

The relative infrequency of infection with *B. proteus* is in striking contrast to its potential seriousness to the afflicted individual. Its peculiar menace is due to its ability to break down the urea of the urine into carbon dioxide and ammonia, the latter of which makes the urine strongly alkaline. The urea is apparently attacked by an enzyme contained in the bacterial cell, since killed and desiccated cultures can split urea, although it is impossible to extract an urease from the living organism (Day and co-workers).

The clinical importance of this alkalinization of the urine was recognized as early as 1901 by Brown, of Baltimore, who reported 5 cases of stone due to infection with urea splitters, for 3 of which *B. proteus* was responsible. Stone formation in such cases is due to the precipitation of the phosphates and carbonates of calcium, magnesium, and ammonia in the alkaline urine. The precipitate may gather about a bit of necrotic tissue (Keyser), fibrin (Lazarus), or a clump of bacteria (Rovsing); or it may become adherent to an ulcer and later drop off (Hager and Magath).

B. proteus is not the only organism which can split urea. Hellström has written extensively about this phase of staphylococcic infection of the kidney; according to Chute, certain strains of streptococci, *B. pyocyaneus, Haemophilus influenzae,* diphtheroids, micrococci, and many strains of *E. coli* also have this faculty. Higgins has stated that 9 per cent of bacilli found in conjunction with nephrolithiasis can decompose urea.

Other known factors in the development of nephrolithiasis in general are summarized in Table I. In all probability the urea splitters can form stones in the absence of all of the systemic and perhaps in the absence of the local factors, although the presence of any or all of the latter increases enormously the danger of stone formation once such organisms gain access to the urinary tract.

INCIDENCE OF INFECTION BY B. PROTEUS IN NEPHROLITHIASIS

B. proteus is found in but a small proportion of renal and ureteral lithiasis. Of 2,537 examples of stone collected from ten reports in the literature (Rovsing, Priestley and Osterberg, Eisenstadt, Lett, Chute, Dege, Smith, Korhonen, Harrington, Chute and Suby), data as to infec-

TABLE I

KNOWN FACTORS IN THE PRODUCTION OF NEPHROLITHIASIS

I. Systemic
A. Deficiency of vitamin A
B. Persistent ingestion of alkali
C. Overconcentration of the urine
D. Increased excretion of calcium
1. Hyperparathyroidism
2. Diseases of bone
a. Osteomyelitis
b. Atrophy (immobilization)
3. Ingestion of acids (?)
E. Increased excretion of uric acid (gout)
F. Cystinuria and xanthinuria
II. Local
A. Stasis of urine
1. Obstructive lesions
2. Recumbency (stagnation in dependent calices)
B. Submucosal necrosis of renal papilla
C. Trauma
D. Foreign body
E. Infection with organisms splitting urea

tion were complete in 2,191. Sixty-five per cent of these were associated with bacteria in the urine. In 6.2 per cent of the whole group and in 11 per cent of those infected, *B. proteus* was found.

The organism occurs relatively more often in the presence of recurrent stones than in primary stones. Swift-Joly and many others find that nearly all recurrent stones are associated with infection and that if post-operative infection with urea splitters occurs, recurrence is almost certain to take place. Chute reported that 13 of 26 recurrent stones were due to infection with *B. proteus,* and Twinem found the organism in 7 of 10 patients with repeated recurrences after operation.

COURSE OF LITHIASIS FROM PROTEUS

Once stones begin to form in the kidneys as a consequence of infection with *B. proteus,* the outlook is black indeed unless stones, predisposing causes (particularly stasis and immobilization in recumbence), and the exciting organism can all be removed. If the urinary tract is normal except for the infection, the *B. proteus* is easily killed by acidification of the urine and the administration of mandelic acid; but if hydronephrosis is present, or if the patient is necessarily immobilized in recumbency as in extensive paralysis or multiple severe fractures the outlook is very grave. In neither instance is it ordinarily possible to acidify the urine; in the latter situation the stasis in dependent calices and the increased excretion of calcium resulting from atrophy of bone may render treatment futile.

TREATMENT

If treatment is to be successful, the presence of *B. proteus* must be discovered and its serious significance appreciated. This can be done

only by proper culture, since it cannot be differentiated from other gram-negative rods in stained smears. It is imperative, therefore, that the urine be cultured in every case of infection and of stone, and that it be cultured at short intervals following any type of operation upon the kidney which involves postoperative drainage of urine to the outside.

After an operation for stone before which the urine was sterile, the greatest pains must be taken to prevent infection with any organism. Since *B. proteus* is a common inhabitant of the bowel, the dressing should be covered with sterile waterproof sheeting to prevent contamination from the bedclothes if the dressing becomes soaked.

If a pelviostomy or nephrostomy is used, special care must be taken in the preparation and handling of the tubing before, during, and after operation. Chute has called attention to the tendency of *B. proteus* to survive attempts at sterilization of rubber tubing containing deposits of urinary salts. This tendency can be circumvented only by constant vigilance. A catheter which has been used for continuous drainage of urine must be soaked in hot soapsuds, then in dilute acetic acid, and then cleaned by drawing gauze through its lumen and rinsing it extensively. If any deposit of salts remains, the catheter should be cut up and discarded. If perfectly clean, it should be autoclaved. Glass connectors and receiving bottles must be cleansed with a mineral acid, rinsed, and autoclaved. The rubber tubing used to connect the catheter to the receiving bottle cannot be sterilized adequately after use because of its length. New, cheap tubing carefully rinsed and autoclaved should be used for each patient and discarded.

It is equally important that the drainage system be kept closed to avoid contamination from the air. A simple method of doing this is to use a two-hole rubber stopper. One hole contains a long glass tube which is connected to the drainage tube. The other holds a short glass tube capped with sterile gauze. The whole assembly is sterile, and the collecting bottle is changed daily (Fig. 1).

Reserve supplies of these kinds should be cultured periodically to make certain that a proper procedure is being followed and is effective.

Immediately after the operation, fluids should be forced to insure diuresis, the patient turned frequently to avoid stasis in dependent calices, and one of the sulfonamides used in small doses from the day of operation as an aid in preventing infection, as advocated by Stalker and Schulte.

The stone should be analyzed at once. If it consists of phosphates and carbonates, it is desirable, as soon as the postoperative reaction has subsided, to acidify the urine to a pH of 5.4 or below and thereafter to give mandelic acid and to limit fluids until any infection has been overcome. Because most preparations of mandelic acid contain ammonia or calcium and because acidification of the urine may increase the excretion of calcium (Albright, Sulkowitch, and Chute), this regime probably should not be continued after sterilization of the urine. If it proves impossible

to acidify the urine, and thereby to sterilize it, or if the stone is of a type formed in acid urine (oxalates, urates), the sulfonamides should be continued until the urine is sterile.

Upon subsidence of the postoperative reaction, the patient should receive an adequate mixed diet with an abundance of vitamins.

Fig. 1.—Apparatus for continuous drainage of urine and continuous irrigation of bladder with 0.8 per cent sulfanilamide.

If the *B. proteus* or another urea splitter is found *before* operation, and if the stones appear soft and crumbly or are multiple, operation probably ought to be deferred until the stones become denser and more discrete, or consolidate, or both, because of the certainty of recurrence around any sand left behind. At operation great care should be taken to remove all fragments; success should be verified by x-rays made on the operating table.

Nephrostomy is imperative to avoid postoperative obstruction, to afford escape for blood and other detritus which might form the nu-

cléus of a new stone, and to permit acid irrigations. The last are intended both to afford an unfavorable culture medium for the urea splitters and to dissolve any sandy material left behind, although the latter is more to be hoped for than expected. The preferred solution is the mixture of citric acid and sodium citrate evolved by Albright, Sulkowitch, and Chute (sodium citrate, 45.2 Gm.; citric acid, 38 Gm.; and distilled water, 1 liter). This may cause considerable irritation and have to be diluted, discontinued, or alternated with saline solution. In suitable cases it may even be used as a drip.

During convalescence sulfathiazole should be given in full doses, substituting sulfanilamide or sulfapyridine if the first is ineffective in killing the organisms.

The nephrostomy should be maintained until the urine is sterile or until stasis is overcome so that the urine can be acidified to a pH of 5.4 and kept there, when mandelate may be started and the tube withdrawn. It is impossible to overemphasize the importance of aseptic handling of the nephrostomy tube and of everything connected with it; it is difficult to convince interns and nurses that a fleeting contact between the open end of the tube and the bedclothes during irrigation or the use of a syringe or solution of doubtful sterility may defeat the whole purpose of the surgical removal of a stone; yet it is so.

By these methods recurrences can be minimized, although Chute found that 74 per cent of patients operated upon for stone in the presence of urea splitters had recurrences within three years. Swift-Joly states that: "If the infection is caused by a urea splitting organism, it is most probable that a secondary phosphatic calculus will form in a short time." He has observed recurrence in 16 per cent of aseptic and 50 per cent of infected renal calculi.

Because of the frequency with which instrumentation precedes infection with *B. proteus,* most such infections can be prevented by proper attention to the details of asepsis in the use of urethral instruments and especially of inlying catheters and cystostomy tubes. In addition, the same regime recommended after lithotomy should be observed during drainage of the bladder; i.e., the use of sulfonamides or of acidification and mandelic acid, an adequate diet and fluid intake and, above all, aseptic handling of sterile tubing and bottles.

CASE REPORTS

Our own material at the University Hospital is too small to permit any statistical computations. In the period from July, 1930, to January, 1940, renal and ureteral calculi were diagnosed 495 times. *B. proteus* was found in the urine on culture in 12 cases (2.4 per cent). Nine of the 12 were admitted during the last four years. This is due in part to the operation of chance, in part to the increasing frequency of urethral instrumentation, and in part to more careful and more frequent bacteriologic studies of the urine, based upon realization of the

serious significance of infections with this organism after painful experiences with the first 3 cases. The cases have been divided, rather artificially, into those following: (1) operations upon the bladder, (2) operations upon the kidney, (3) use of inlying catheter in patients profoundly ill, and (4) apparently spontaneous infections.

CASES FOLLOWING OPERATION UPON THE BLADDER

H. N. (No. 608824), aged 22 years, had a cystostomy in September, 1932, by another physician because of a contracted bladder of unknown etiology with bilateral hydronephrosis and hydroureter. Six weeks later he was admitted with the tube clogged; he had multiple calculi in the left kidney and *B. proteus* in the urine. By January, 1933, he had bilateral calculi which were growing rapidly; left pelviolithotomy and nephrostomy in March, 1933, were followed by prompt recurrence. Despite acid irrigations, the use of neoarsphenamine and ketogenic diet, and the passage of many stones from both sides, the patient slowly failed and died on July 28, 1934. Necropsy disclosed interstitial cystitis, bilateral hydronephrosis, pyelonephritis with abscesses, and nephrolithiasis.

Comment.—This was my first experience with what might be called "malignant" nephrolithiasis due to implantation of *B. proteus* into hydronephrotic kidneys. The lessons learned then have been slowly sinking in ever since.

S. B. (No. 616637), aged 31 years, admitted in September, 1934, had an encrusted cystitis with *E. coli*, staphylococci, and diphtheroids. It had resisted every form of conservative treatment for five years, wherefore presacral neurectomy and curettage of the bladder were done after admission. There was temporary benefit, but six weeks later she returned with hydronephrosis and acute bilateral pyelonephritis due to *B. proteus*. Bilateral pelviolithotomy and permanent nephrostomy were finally necessary.

She died under unknown circumstances outside the hospital three years later.

Comment.—*B. proteus* apparently followed the cystostomy tube to the bladder and then regurgitated to the kidneys. Stones formed and grew rapidly; their removal and nephrostomy were inadequate to control the process despite energetic irrigations and the use of all available antiseptics.

L. H. (No. 634521), aged 21 years, admitted in January, 1935, from another hospital, had been in an automobile accident six months before. He had a fractured pelvis, suprapubic, perineal, and rectourethral fistulas, and multiple calculi in the right kidney and bladder, infection with *B. proteus*, and malnutrition.

Despite a series of efforts, including urinary antiseptics, litholapaxy, colostomy, irrigations, and dietary management, he died in August, 1936, of chronic pyelonephritis, nephrolithiasis, uremia, and amyloidosis.

Comment.—The initial injury was very severe; the complications more so; every measure tried proved ineffective. All 3 of these cases emphasize, by default, the value of the sulfonamides.

D. M. (No. 686663), aged 7 years, admitted Oct. 30, 1939, had a large ureterocele with 300 c.c. of residual urine infected with streptococci and *Staphylococcus albus*. There was bilateral duplication of pelves and ureters with one functionless segment on each side and regurgitation up the ureters.

The ureterocele was excised and cystostomy made on Nov. 7, 1939, and he was sent home with drainage aimed at improving renal function. In February, 1940, he had *B. proteus* in the urine, a calculus in the functioning segment on the right, three in its ureter, and two in the functioning segment on the left (Fig. 2). In March, 1940, right pelviolithotomy, nephrostomy, and heminephrectomy were done, and *B. proteus* was eradicated later with sulfathiazole. A drip of citric acid-sodium citrate was then attached to the nephrostomy; in three weeks the ureteral calculi were gone.

Fig. 2.—Case D. M. Calculi following infection with *B. proteus* through a cystostomy.

In August, 1940, the left renal calculi passed into the ureter; left heminephrectomy and nephrostomy were done. In October, 1940, the citrate drip was started on the left; in eleven days the stones and *B. proteus* were gone (Fig. 3). The nephrostomies are being maintained pending recovery of the bladder.

Comment.—This is a striking demonstration of the value of sulfathiazole and the citric acid-sodium citrate combination; it is a question whether the child has enough renal function to permit growth and whether the terrifically damaged bladder will ever become useful.

K. D. (No. 694539), aged 36 years, admitted on April 23, 1940, had a recurrent giant left renal calculus with pyuria and *B. proteus*. A bladder tumor had been

fulgurated elsewhere in 1931; a branched left renal calculus had been removed by another surgeon in 1934, at which time cultures showed *E. coli* and streptococci; a fistula had been present intermittently since.

Left nephrectomy on April 27, 1940, was followed by recovery. Both sulfanilamide and sulfathiazole were used postoperatively. On Nov. 14, 1940, the urine and KUB were negative and the patient symptom free.

Comment.—Unilateral calculous pyonephrosis due to *B. proteus* presents no special problem other than eradication of the organism from the bladder postoperatively.

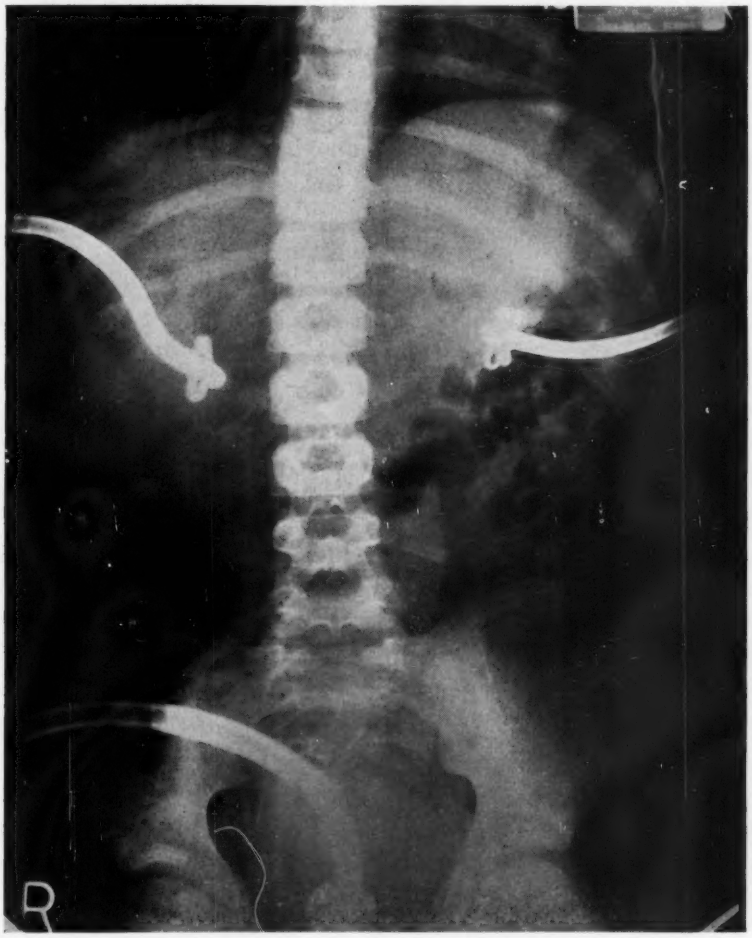


Fig. 3.—Case D. M. Calculi dissolved by continuous irrigation with citric acid and sodium citrate through nephrostomies.

CASES FOLLOWING OPERATION UPON THE KIDNEYS

V. T. (No. 636931), aged 25 years, was admitted on March 28, 1935. Six years before he had received intensive local treatment elsewhere for gonorrhea. For two years he had had a mild lumbar backache. The general state was excellent. The urine contained pus and staphylococci; KUB showed a branched stone on the right, two bean-sized calculi in the left pelvis, and one in the left lower ureter.

On April 12, 1935, left pelviolithotomy and pelviostomy, and on April 30, left ureterolithotomy were performed. Irrigations with 1 per cent silver nitrate were

carried out. On May 16, 1935, the urine from both kidneys contained *B. proteus*. Nevertheless, right nephrolithotomy and nephrostomy were done in September, 1935. Both pelves were then lavaged weekly with silver nitrate on eleven occasions. The ketogenic diet and neoarsphenamine were without effect. In January, 1936, culture showed *B. proteus* on both sides, after which he abandoned treatment.

On Dec. 3, 1940, he was well but had an occasional white cell and *E. coli* in the urine. The KUB was negative.

Comment.—This patient was evidently infected by staphylococci during treatment for gonorrhea and developed four stones. *B. proteus* was introduced into both sides by drainage tubes after lithotomy. Nevertheless, because he was robust, he had no systemic disease, no stasis, and resumed normal activity, *B. proteus* disappeared spontaneously. That he is well five and one-half years later is due at least as much to good luck as to good management. He is now under treatment to eradicate *E. coli*.

B. H. (No. 671576), aged 28 years, admitted Nov. 21, 1938, had left renal colic of two months' duration. There was a stricture of the left ureteropelvic junction with a small hydronephrosis and a minute shadow in the right renal area. The urine was sterile. Dilatation of the left ureter being ineffective, a Y-plasty was done on Nov. 22, 1938. In a culture made on the day of operation, *B. proteus* was found in urine from the bladder; its significance was not appreciated.

Fifteen days after operation there was a right renal colic. A small calculus was pushed from the upper ureter into the pelvis, urine from which contained *B. proteus*. Thereafter acidification of the urine was impossible and sulfanilamide ineffective. Stones were passed intermittently from the right until readmission on Aug. 23, 1939, with fever and right renal pain. At operation fibrin and sandy material were removed from the inflamed right kidney, and nephrostomy was done. Bleeding occurred into the wound that night, and the patient died despite transfusion, evacuation of clots, and packing.

At necropsy, the hemorrhage was found to have come from an ureteral vessel. The left kidney was normal except for a little scarring.

Comment.—B. proteus was introduced at cystoscopy and overlooked. There is evidence that a silent calculus was present on the right before operation, but it was the introduction of the organism that led indirectly to death which could have been prevented by the nephrectomy which seemed at the time unwise.

H. J. (No. 654859), aged 38 years, was admitted Nov. 9, 1937, for disabling bilateral backache of long standing, not relieved by ureteral dilatation, and due to low-grade bilateral obstruction at the ureteropelvic junction, with sterile urine. In November, 1937, a right Y-plasty was done. Recovery was uneventful, but a month later urine drained from the wound until a small stone was passed. *B. proteus* was then found in the urine but responded to sulfanilamide.

Left Y-plasty was done in June, 1938. Recovery was uneventful, but he returned in two months with a left renal colic, a stone 2 cm. in diameter in the left kidney, and pyuria with *B. proteus*. On August 9 left pelviolithotomy was performed and the urine sterilized by 6 Gm. of sulfanilamide daily for three weeks.

In June, 1940, excretory urography showed no calculi, and in August the urine was sterile.

Comment.—One wonders at the temerity of both patient and surgeon in wanting a second operation after the experience with the first, yet sulfanilamide unquestionably saved the day.

M. B. (No. 675383), aged 58 years, was admitted Feb. 6, 1939. For two years he had had left renal colics and pyuria, due to bilateral multiple calculi with pus and diphtheroids in the urine. After left pelvionephrolithotomy and nephrostomy in February, 1940, *B. proteus* was somehow introduced, and although recovery was good, recurrence was prompt. Because of the presence of hydronephrosis and calculi, it has been impossible to destroy the organism. Curiously enough the patient has remained symptom-free, although his outlook is not good.

Comment.—Operation defeated by the introduction of *B. proteus.*

CASES DUE TO THE INLYING CATHETER

E. J. (No. 686081), aged 27 years, was placed in the respirator because of bulbar poliomyelitis with retention of urine in September, 1939. The urine on admission contained pus, *E. coli,* gamma streptococci, and *Staphylococcus albus.*

Despite many attempts at acidification, the use of sulfanilamide, and sufficient recovery to permit sitting up and removal of the catheter, *B. proteus* appeared first on Feb. 18, 1940, resisted treatment, and caused death on April 14, 1940. Necropsy disclosed acute bilateral pyelonephritis with multiple abscesses and calculi.

Comment.—Better care of the inlying catheter would have prevented this all too common outcome in a patient with temporary paralysis of the bladder. Such occurrences, so frequent after injuries to the spinal cord, are a reflection upon the handling of patients with paralyzed bladders.

J. S. (No. 685656), aged 47 years, was confined for several months in another hospital because of fractured ribs, spine, and skull. He was at first unconscious and had an inlying catheter. In August, 1939, two months after discharge, left renal colics led to admission to the University Hospital. In September he had a branched calculus on the right and a stone 2 cm. in diameter on the left (Fig. 4). Left pelviolithotomy, nephrostomy, acid irrigations, and sulfathiazole killed the *B. proteus* on the left. In January, 1940, the same procedure was followed on the right, and he was discharged, free from *B. proteus,* on Feb. 24.

In June, 1940, he was symptom-free, x-ray was negative, and the clear urine contained a "coagulase negative" (presumably nonpathogenic) staphylococcus.

Comment.—The apparently successful issue depended upon disappearance of the predisposing causes (immobilization, bone atrophy, inlying catheter) and careful postoperative eradication of the organism.

F. H. (No. 691126), aged 39 years, was admitted in shock due to right renal colic and fever in March, 1940. She proved to have a bilateral duplication of the renal pelvis and ureter with calculi in the right upper segment and its ureter, and in the left lower segment, both infected with *B. proteus.* Her condition was precarious. The blocked right upper segment was drained with an inlying catheter, and the ureteral stone was finally pushed into the pelvis. Right pelviolithotomy and nephrostomy were done on April 20, 1940. The *B. proteus* was killed by irrigations and sulfathiazole.

On July 15, 1940, left heminephrectomy was done, because the stone was crumbly and adherent. *B. proteus* was absent from the urine on both sides at discharge, but on Nov. 30, 1940, she had three small calculi in the right lower (unoperated) pelvis, and the urine contained *E. coli;* she was pregnant.

Comment.—The calculi in the lower segment probably formed before the *B. proteus* was eradicated. The persistence of *E. coli* and the past history make therapeutic abortion and sterilization imperative.

Fig. 4.—Case J. S. Calculi due to infection by *B. proteus* through an inlying catheter.

APPARENTLY SPONTANEOUS

Mrs. F. L. (No. 699880), aged 63 years, was admitted on Oct. 10, 1940, because of severe pain in the left flank of two months' duration. There was no history of instrumentation. She was obese and quite feeble and proved to have a left calculous pyonephrosis with purulent urine containing *B. proteus.* Because of her poor general state, nephrostomy was done on Oct. 15, 1940, and her general condition improved. Nephrectomy was done on Dec. 18, and recovery was satisfactory.

Comment.—Unilateral destructive disease with a sound opposite kidney presents no special problems and has but one solution.

SUMMARY

Thirteen cases of nephrolithiasis secondary to infection by *B. proteus* have been reported. The organism, resident in the bowel, is usually introduced into the urinary tract by or through the catheter, forms ammonia from the urea of the urine, thus alkalinizing the urine and precipitating the phosphates and carbonates of calcium, ammonia, and magnesium, especially in the presence of stasis, recumbency, and increased excretion of calcium.

In 11 of the 13 patients (84 per cent) it is known to have been introduced by catheters, usually employed as nephrostomies or cystostomies. In 2, congenital anomalies of the urinary tract were present. In 9 (70 per cent), the calculi were bilateral; 2 grew very rapidly under observation. Five (38 per cent) of the patients died, 4 as a direct result of the infection and lithiasis, and 1 from a surgical accident.

Treatment was entirely futile in the earlier cases but is gradually improving for four reasons: the development of effective urinary antiseptics (sulfanilamide and especially sulfathiazole) and the citrate-citric acid irrigant; a clear understanding of the mode of entrance of the organism into the urinary tract; an appreciation of its extraordinarily serious potentialities; and comprehension of the role of predisposing factors such as stasis and recumbency.

As a result, 7 patients have been apparently cured of the infection, and 6 of the stone-forming tendency by a combination of operation and sulfonamides, and in suitable cases, irrigations with citrate-citric acid.

Three must be classified as cures more or less by default, since 2 followed nephrectomy for unilateral disease, and 1 occurred spontaneously after removal of calculi. Two of the "cured" patients have *E. coli* but not pus in the urine, and 1 has calculi in the unoperated segment of a double kidney, apparently having started these stones before the organism was eradicated.

The real solution of the problem lies, however, not in removing stones, relieving stasis, and curing infection, but in preventing the entrance of the organism into the urinary tract by adequate, painstaking, and persistent attention to the proper sterilization of catheters and their adjuncts, to their aseptic introduction and fixation, and above all, to the proper care of systems draining urine from the body. To this end, educational activities by informed urologists are imperative.

REFERENCES

Albright, F., Sulkowitch, H. W., and Chute, R.: Nonsurgical Aspects of the Kidney Stone Problem, J. A. M. A. **113**: 2049-2052, 1939.

Brown, T. R.: On the Relation Between the Variety of Microorganisms and the Composition of Stone in Calculous Pyelonephritis, J. A. M. A. **36**: 1395-1397, 1901.

Cabot, H.: Infections of the Kidney in Modern Urology, Philadelphia, 1936, Lea & Febiger.

Chute, R.: Significance of Urea Splitting Organisms in Formation of Urinary Calculi, New England J. Med. **219**: 1030-1032, 1938.

Chute, R., and Suby, H. I.: Prevalence of Urea Splitting Bacterial Infections of the Urinary Tract in the Formation of Calculi, J. Urol. **44**: 590-595, 1940.

Day, A. A., Gibbs, W. M., Walker, A. W., and Jung, R. E.: Decomposition of Urea by Bacillus Proteus, J. Infect. Dis. **47**: 490-502, 1930.

Dege, H. A.: Beobachtungen an den Harnsteinkranken der Jenaer Chirurgischen Klinik in den letzten 10 Jahren, Arch. f. klin. Chir. **191**: 632-679, 1938.

Eisenstaedt, J. S.: Certain Tangible Factors in the Etiology of Renal Calculi, Surg., Gynec. & Obst. **53**: 730-734, 1931.

Hager, B. A., and Magath, T. B.: The Formation of Vesical Calculi, J. A. M. A. **90**: 266, 1928.

Harrington, H. L.: A Clinical Study of 480 Cases of Urinary Lithiasis, J. Urol. **44**: 507, 1940.

Hauser, G.: Ueber die Fäulnisbakterien und deren Beziehungen zur Septikämie, Leipzig, 1885.

Hellström, J.: Staphylococcus Stones, A Clinical Study of 90 Cases, Stockholm, 1936, P. A. Norstedt & Sons.

Higgins, C. C.: Factors in Recurrence of Renal Calculi, J. A. M. A. **113**: 1460-1465, 1939.

Keyser, L. D.: Recurrent Urolithiasis; Etiological Factors and Clinical Management, J. A. M. A. **104**: 1298-1306, 1935.

Korbonen, A.: Ueber die Harsteine, Acta Soc. med. fenn. duodecim **22**: 1-184, 1936.

Kretschmer, H. L., and Mason, L. W.: Bacillus Proteus Septicemia; Report of Two Cases With Recovery, J. A. M. A. **92**: 1734-37, 1929.

Lazarus, J. A.: Trauma as an Etiological Factor in Renal Stone Formation, Urol. & Cut. Rev. **43**: 529-535, 1939.

Lett, H.: On Urinary Calculus With Special Reference to Stone in the Bladder, Brit. J. Urol. **8**: 205-232, 1936.

Meyerhof, M.: Ueber einige biologische und tierpathogene Eigenschaften des B. Proteus (Hauser), Centralbl. f. Bakteriol. **24**: 18, 55, 148, 1898.

Priestley, J. T., and Osterberg, A. E.: The Relationship Between the Chemical Composition of Renal Calculi and Associated Bacteria, J. Urol. **36**: 447-459, 1936.

Rovsing, T.: Renal Calculi, Ztschr. f. urol. Chir. u. Gynäk. **12**: 358-384, 1923.

Schulte, T. L.: Newer Methods in Study of Bacteriology of Urinary Tract; Preliminary Report, Proc. Staff Meet., Mayo Clin. **14**: 249-254, 1939.

Scott, W. W.: Blood Stream Infections in Urology, Report of 82 Cases, J. Urol. **21**: 527-566, 1929.

Scott, W. W., and Sandholzer, L. A.: Bacteriological and Clinical Study of Bacillary Infections of Urogenital Tract, J. Urol. **42**: 182-196, 1939.

Smith, G. G.: Renal Infection and Nephrolithiasis, Surg., Gynec. & Obst. **68**: 526-533, 1939.

Stalker, L. K., and Schulte, T. L.: A Bacteriologic Study in Postoperative Retention of Urine, Proc. Staff Meet., Mayo Clin. **14**: 730, 1939.

Streng, H. O.: Über das Vorkommen des B. Proteus in den Harnwegen, Acta Soc. med. fenn. duodecim **19**: 1-18, 1936.

Swift-Joly, J.: Stone and Calculous Disease of the Urinary Organs, St. Louis, 1931, C. V. Mosby.

Topley, W. W. C. and Wilson, G. S.: The Principles of Bacteriology and Immunity, Philadelphia, 1938, William Wood & Co.

Twinem, F. P.: A Study of Recurrence Following Operations for Nephrolithiasis, J. Urol. **37**: 259, 1937.

EXTRADURAL HEMORRHAGE IN THE POSTERIOR FOSSA

CLAUDE C. COLEMAN, M.D., AND J. L. THOMSON, M.D.,
RICHMOND, VA.
(From the Department of Neurological Surgery, Medical College of Virginia)

DISCUSSION of extradural hemorrhage in the literature has been restricted almost exclusively to those clots which result from laceration of the trunk of one of the branches of the middle meningeal artery. Clots from this source cause rapid and direct cerebral compression. In typical cases they are readily recognized, but inasmuch as they do not always develop classical symptoms, the mortality continues high because of late diagnosis.

Extradural hemorhage from a lacerated sinus of the cerebral dura is rare, but some recognition is given in the literature to the possibility of clots from this source.

Little attention has been given to extradural hematoma in the posterior fossa where the arterial supply of the dura is scanty. A clot forming between the dura and bone of the posterior fossa arises from a laceration of one of the dural sinuses.

A review of the literature fails to record any clinical discussion of these cases prior to McKenzie's[1] article in 1938. This writer describes such a case in a child recognized only at autopsy where an extradural clot measuring 2 cm. in thickness and 5 cm. in diameter was found over the right cerebellar hemisphere. He also relates the history of two adult patients, each of whom had extradural cerebellar collections of blood as extensions from extradural clots over the cerebral hemispheres. A posterior fossa operation was performed on one patient who died shortly afterward. The other patient had a temporal exploration and the posterior fossa clot was found at autopsy.

Lecount and Appelbach[2] in 1920 reporting on 504 autopsied cases of skull fracture had 8 cases of extradural hemorrhage in the posterior fossa. The source of hemorrhage in each instance was from one of the transverse sinuses and the clot did not exceed 50 Gm. Likewise, Vance[3] in 1927 recorded 512 autopsies of skull fracture and noted 4 cases of extradural hemorrhage from torn lateral venous sinuses. However, it was not clearly stated whether these clots were entirely confined to the posterior fossa or extended upward over the occipital lobes. Mayfield[4] recently had a patient in whom a cerebellar clot was suspected but who died before the posterior fossa could be explored. Autopsy revealed an extradural cerebellar hematoma.

The present case is reported in considerable detail because of the rarity of the condition, the fact that we found no reported case which

Received for publication, March 15, 1941.

recovered, and to emphasize the features of a clinical picture which is highly suggestive of extradural hemorrhage in the posterior fossa. Careful study of the case led to a correct preoperative diagnosis and the appropriate operative procedure was followed by complete recovery of the patient.

CASE REPORT.—(No. 73891.) A previously healthy negro male, 9 years of age, was admitted to Saint Philip Hospital, Dec. 18, 1939, and discharged Jan. 3, 1940.

Present Illness.—Two days before admission the child fell from a moving truck, striking the back of his head, but was not rendered unconscious. Shortly afterward he was brought to the emergency room of the hospital where examination showed an alert and cooperative child, the only sign of injury being a small hematoma in the left occipital region. All reflexes were normal and the patient was discharged. He was returned in about twenty-four hours because of headache, some drowsiness, and because he had vomited once or twice. Again the neurological examination was essentially negative. The child was taken home and was brought to the hospital again the following night. This time he was moderately drowsy, occasionally very restless, complained of headache and had vomited several times. There were still no abnormal neurological findings. However, the patient was admitted to the hospital for observation. Fifteen hours later (morning of the third day following accident), the child was very drowsy but moved readily on painful stimulation. He would persistently lie on the left side and when turned on his back would again promptly turn to the left side.

On examination the hematoma in the left occipital region was still present. The neck was spastic and the patient cried out when attempts were made to flex it. The pupils were equal, moderately dilated and reacted to light. There was no nystagmus or strabismus. All cranial nerves were normal including the optic disks. The patient moved all extremities equally well, but there was definite generalized hypotonia. The biceps, triceps, knee and ankle jerks were now entirely absent. The Babinski sign was absent. The general physical examination was essentially normal. The blood Wassermann test was positive. X-ray examination of the skull in the anteroposterior view showed a long linear fracture extending from the lamboidal suture downward into the foramen magnum in the midline (Fig. 1).

The child was now obviously seriously ill and an immediate operation seemed advisable. The operative site was largely determined by the sequence of events which had taken place since the accident. Briefly, the child was not stuporous but had been unconscious, the neck was spastic and passive motion was very painful. He invariably lay on the left side, hypotonia developed and later areflexia appeared. After these facts were established and knowing that a fracture of the occipital bone was present, it seemed most likely that a blood clot was present in the posterior fossa causing cerebellar compression and obstructive hydrocephalus.

Operation (J. L. T.), Dec. 19, 1939.—Under ether anesthesia, bilateral anterior parietal burr openings were made to rule out possible clots over the cerebral hemispheres. The left lateral ventricle was tapped and 30 c.c. of clear ventricular fluid was obtained under pressure. The needle was withdrawn without removing more fluid. The hydrocephalus gave added proof that an obstruction was present in the posterior fossa. Consequently, the patient was prepared for bilateral burr openings of the posterior fossa. An opening was made over the center of the right fossa and immediately about 10 c.c. of old, thin, dark blood escaped under marked pressure. An organized blood clot was readily visible beneath, necessitating an extension of the scalp incision in a bow-shaped outline and removing the bone over the right and left fossae in order to expose the hematoma (Fig. 2). The early

organized hematoma was then removed with suction and by pulling adherent portions away from the dura. The clot was at least 3 cm. thick near the midline and had compressed the midline structures and right cerebellar hemisphere considerably more than the left. An inspection of the borders of the hematoma showed that it had extended on the right, lateralward to the sigmoid sinus. Above, the dura enclosing the lateral sinus was stripped from the bone near the torcular, while on the left, the edge of the clot was near the sigmoid sinus, and below it had extended to the foramen magnum (Fig. 3). As a small portion of the clot was being pulled from

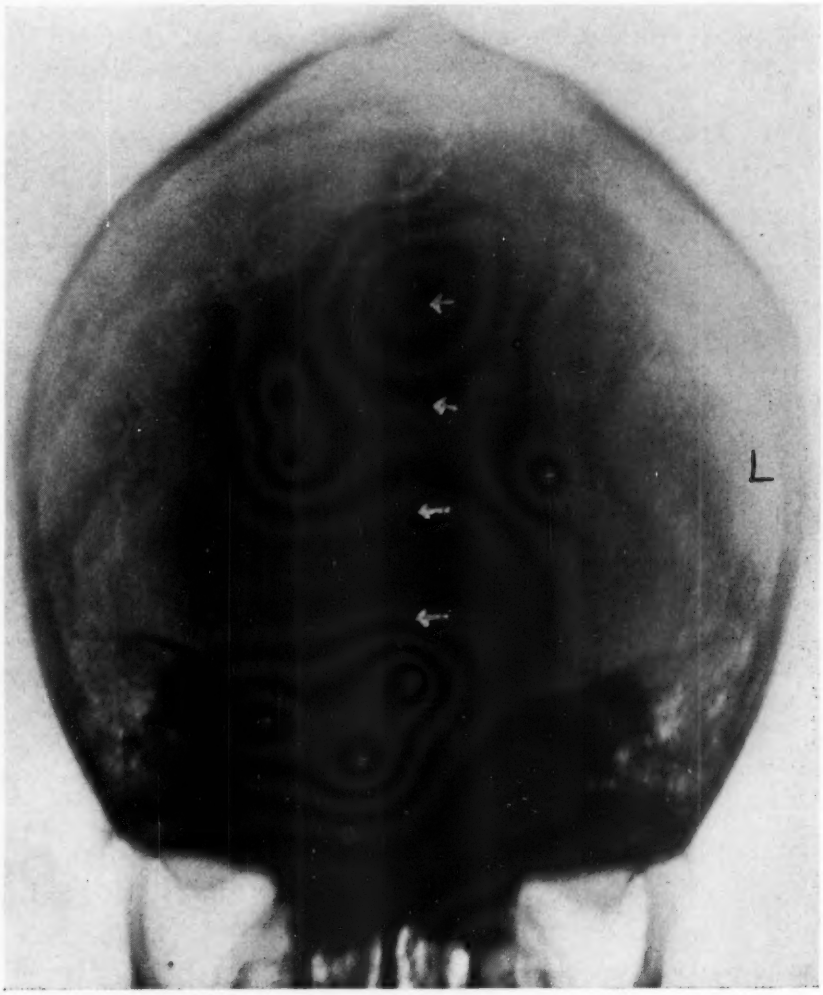


Fig. 1.—X-ray film showing long linear fracture from the inion to the posterior border of the foramen magnum in the occipital bone. Fracture line indicated by arrows.

the torcular, there was profuse bleeding which stopped upon releasing the tension. It was therefore concluded that the torcular Herophili had been torn when the skull was fractured and that the lacerated venous channel was the source of the hemorrhage. When all of the hematoma had been removed, the contents of the posterior fossa re-expanded and began pulsating. Immediately the noisy and irregular respiration became quiet and even. The wound was closed in layers with interrupted black silk. One rubber tissue drain was placed in the right extradural space and was removed twenty-four hours later.

The patient reacted promptly from the anesthesia and four hours later could talk coherently but was moderately drowsy. Improvement was continuously satisfactory so that he was up about the ward on the eleventh postoperative day. Examination showed that the wound had healed by primary intention. There was no stiffness of the neck. The cranial nerves were normal. There was normal muscular tone of the extremities. All of the deep and superficial reflexes were present, equal and normally active. The Babinski sign was absent. There was no ataxia. The child was discharged sixteen days after admission. When seen in the out-patient department two weeks later the examination was negative and his mother stated that he seemed normal in all respects. The patient was last seen on Jan. 21, 1941. At that time he had no complaint, the neurological examination was negative, and he appeared to have no residual impairment.

Fig. 2.

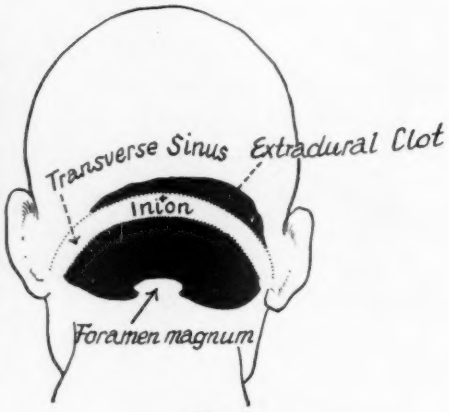


Fig. 3.

Fig. 2.—Appearance of incision fifteen days after operation for evacuation of extradural hemorrhage from the posterior fossa.

Fig. 3.—Diagrammatic view of the size and location of the clot in the posterior fossa.

The relatively slow onset of symptoms in this case, requiring more than sixty hours for drowsiness to appear, was caused by obstruction of the ventricular system by the slowly forming clot, rather than by direct pressure of the clot on the cerebellum. A hematoma from sinus origin forms slowly because the venous pressure within the sinus is only about 4 to 6 mm. of Hg. Since there are no large arterial vessels on the dural surface of the posterior fossa, it is safe to assume that all surgical clots in this region are of venous origin. Therefore, a rather long latent period, possibly in terms of days, may intervene between the time of injury and the onset of symptoms indicating the presence of a clot.

Before the diploe have formed in the skull of a child the dura is more tightly adherent to its inner surface than in an adult. Should a fracture line cross a venous sinus in the occipital fossa a tear in a sinus of

the tightly adherent dura may occur. The transient displacement of the bone fragments strips the dura from the bone, thus allowing extravasation of venous blood between the bone and dura. It seems unlikely that a tear in a sinus in this location can occur without a fracture of the skull. From reports in the literature and the experience of the present case, it may be said that a hematoma of the posterior fossa does not occur in the absence of skull fracture. It is difficult to say why patients with rapidly expanding lesions of the posterior fossa prefer to lie on one side, usually on the side of the lesion. A suggestion is that an attempt is being made to keep the weight of the clot off of the vestibular nuclei in the vermis and vagal nuclei in the brain stem, thereby preventing reflex vertigo and vomiting. This phenomenon of forced position has been observed on a number of occasions at this clinic. Some years ago a young boxer received a light blow on the back of his head and about twenty-four hours later became very drowsy. He would persistently lie on his side and when turned on his back would vomit violently and rapidly turn to the side again. At operation by one of us (C. C. C.) a large acute intracerebellar hematoma was removed and the patient made an uneventful recovery.

Frequent neurological examinations are necessary, to observe the appearance and progression of hypotonia and hyporeflexia which becomes evident as drowsiness increases. These cerebellar signs in the presence of nuchal rigidity are most important aids in making a correct diagnosis. Even though this type of lesion is extremely rare it should be considered in a drowsy patient who has evidence of cerebellar compression and a fracture of the occipital bone.

It is important to stress the fact that morphine should not be given or a lumbar puncture performed in the management of suspected extradural hemorrhage in the posterior fossa. Morphine notably suppresses respiration in the already drowsy patient and is dangerous when increased intracranial pressure is present. Morphine should never be given until the intracranial pressure has been controlled. Lumbar punctures may be helpful in the diagnosis of nonoperative cases of acute head injury, but the procedure is definitely contraindicated if an extradural hemorrhage is suspected, because sudden disturbance of intracranial relations by withdrawing cerebrospinal fluid may cause a shift of or pressure upon the brain stem with damage to important centers. Since the primary effect of an acute extradural hemorrhage is to produce increased intracranial pressure and since bloody spinal fluid does not definitely rule out such a clot, one easily realizes that lumbar puncture adds little information to the history and neurological examination.

The diagnostic criteria for recognition of an extradural hematoma in the posterior fossa are as follows: There is a history of a blow on the back of the head severe enough to produce a fracture of the skull but

which may or may not cause unconsciousness. This is followed by headache of gradual increasing severity and is usually accompanied by nausea and vomiting. Drowsiness and restlessness appear and progress until the patient lapses into unconsciousness. However, during the drowsy state several things may be noted. The patient prefers to lie on one side and will promptly return to the same side when placed on his back. Nuchal rigidity develops, nystagmus may or may not be present, and the deep reflexes disappear. As unconsciousness deepens, generalized hypotonia develops, the pulse and respiration become irregular and death is imminent unless there is prompt surgical intervention with removal of the clot.

REFERENCES

1. McKenzie, K. G.: Brit. J. Surg. 26: 346, 1938.
2. Lecount, E. R., and Appelbach, C. W.: J. A. M. A. **74**: 501, 1920.
3. Vance, B. M.: Arch. Surg. **14**: 1023, 1927.
4. Mayfield, F. H.: Personal communication.

EXPERIMENTAL STUDIES ON ALIMENTARY AZOTEMIA

II. The Relative Importance of the Plasma and Erythrocyte Fractions of Absorbed Blood*

Henry N. Harkins, M.D., Ph.D., and C. Frank Chunn, M.S., M.D.,
Detroit, Mich.

(From the Division of General Surgery, Henry Ford Hospital)

THE occurrence of an increased blood urea nitrogen concentration in certain cases of intestinal hemorrhage, particularly in patients with bleeding peptic ulcer, has considerable prognostic significance. In previous papers,[1, 2, 3] the literature was reviewed on this subject of azotemia following gastrointestinal hemorrhage in patients and in experimental animals and the term alimentary azotemia was introduced as a more definitive name for this condition and one comparable to those applied to other similar processes. This earlier work agreed closely with that of Schiff and associates[4] and with slight variations with that of Kaump and Parsons.[5]

Most observations on human patients and experimental work on animals so far reported have employed the use of whole blood in the study of alimentary azotemia. Schiff and co-workers[4] observed an appreciable degree of alimentary azotemia in one human subject following the ingestion of 1.8 kg. of lean meat. That the cells rather than the plasma are the active principle in producing this type of azotemia was first stated in preliminary reports by one of us (C. F. C.)[6] in 1940, and later by the other (H. N. H.)[7] and by Boals and both of us[8] in 1940. In a later paper, Yuile and Hawkins[9] in 1941 reported independent data confirming this conclusion.

In consideration of this and other observations made in our earlier experiments, it occurred to us that the etiology of alimentary azotemia should be further studied by breaking the whole blood down into its component parts to determine if possible which fraction or combination of fractions was responsible for the production of alimentary azotemia.

EXPERIMENTAL

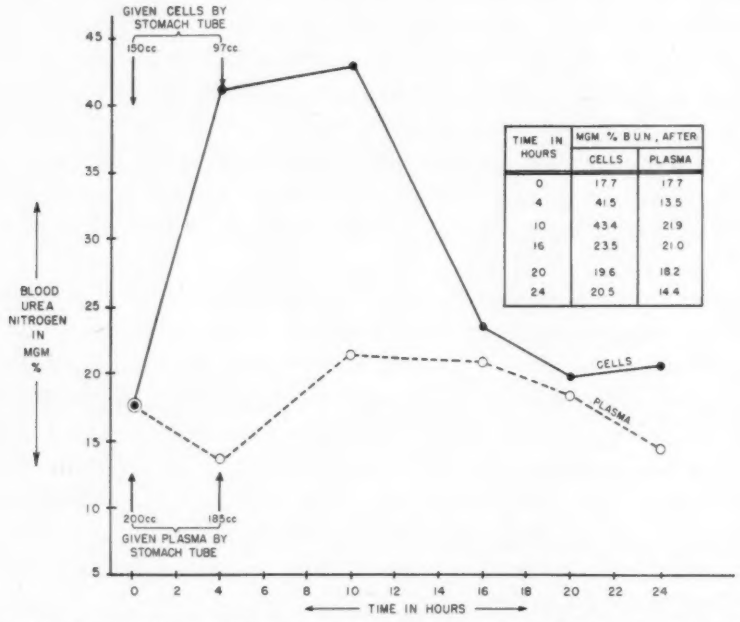
Method.—A large quantity of citrated beef blood was separated into the plasma and cell fractions by centrifuging. Five dogs were given varying amounts of beef cells by stomach tube and five dogs were given beef plasma in the same manner. The dogs were young, healthy, and apparently free from renal disease.

Urea nitrogen determinations, using essentially the same method as that of Van Slyke and Cullen,[10] were made from samples taken at 2:00

*A portion of the thesis submitted by C. Frank Chunn to the Graduate School of the University of Michigan in partial fulfillment of the requirements for the Degree of Master of Science in Surgery.

Received for publication, March 18, 1941.

and 8:00 A.M., 12:00 noon, and at 4:00 and 8:00 P.M. Blood was drawn for analysis from the jugular vein of each dog during a control period of from one to three days preceding each series of experiments and continued twenty-four hours after the curve had returned to normal. The dogs were given their usual amount of food divided into four small feedings daily. Water was given freely. As in our previous experiments on the effects of whole blood, when the normal blood urea nitrogen curve was established, the dogs in Group A were given beef blood cells by stomach tube in divided doses at intervals and the dogs in Group B were similarly given beef plasma.



TIME IN HOURS	MGM % BUN, AFTER	
	CELLS	PLASMA
0	17.7	17.7
4	41.5	13.5
10	43.4	21.9
16	23.5	21.0
20	19.6	18.2
24	20.5	14.4

Fig. 1.—The comparative effects of blood cells and blood plasma in the production of alimentary azotemia in dogs.

Results: Relative Effects of Plasma and of Red Blood Cells.—The five dogs receiving the beef blood cells all showed an elevation of blood urea nitrogen above normal within four hours and a maximum concentration of blood urea nitrogen at various intervals between five and twelve hours, depending on the amount and number of doses given. After administration of the last dose of cells, the return to normal of the blood urea nitrogen required from twelve to seventeen hours as seen in Fig. 1 which represents the result in a typical experiment.

The five dogs that received beef plasma by stomach tube showed a longer interval between the first administration of plasma and the initial rise of blood urea nitrogen. The rise occurred in four experiments at four, eight, ten, and eleven hours respectively. In one dog receiving plasma there was no deviation from the normal blood urea nitrogen curve throughout the experiment. The maximum blood urea nitrogen concentration was apparent in the four dogs which showed a rise at

intervals of from eight to eleven hours, one dog showing no elevation as mentioned. The return of the blood urea nitrogen to normal following the last administration of plasma required from five and one-half to twenty hours as shown also in Fig. 1.

It was noted that with the exception of a small portion of the curves of Dogs 3 and 5 (not shown in Fig. 1) the blood urea nitrogen was always higher for the animals receiving blood cells than for the animals receiving blood plasma. This occurred even when the doses of plasma were double that of cells. In one experiment where the maximum concentration of blood urea nitrogen of the plasma-fed dog attained the same elevation as that of the cell-fed dog on the first day only, a total of only 371 c.c. of blood cells was given as compared to 489 c.c. of blood plasma preceding the maximum elevation of blood urea nitrogen. In the other experiment where the blood urea nitrogen elevation persisted a little longer in the plasma-fed animal, the dosage of plasma was 700 c.c. as compared to only 395 c.c. of cells. The other three experiments revealed a much lower blood urea nitrogen concentration for the animals given plasma, and as mentioned before, in one experiment, there was no elevation even though the animal was given 600 c.c. of plasma in 200 c.c. doses at four-hour intervals.

Additional Experiments on Rats.—Deviating from our usual procedure, two adult albino rats weighing from 350 to 400 Gm. were given 15 c.c. of blood cells by stomach tube and at the same time 15 c.c. of physiologic saline solution intraperitoneally to combat any possible degree of dehydration. Three control rats received only the 15 c.c. of of saline solution intraperitoneally. A control rat was killed at this time and 3 c.c. of blood taken from the heart showed a blood urea nitrogen of 14.7 mg. per cent. Six hours later a blood cell-fed rat was killed and 3 c.c. of heart blood recovered. The blood urea nitrogen was 47.6 mg. per cent, and the control at this time revealed a blood urea nitrogen concentration of 13.4 mg. per cent. This was repeated with the second experimental rat in eighteen hours, at which time the blood urea nitrogen was 29.8 mg. per cent, as seen in Fig. 2.

Effect of Ingested Blood on Rectal Temperature and General Condition.—Rectal temperatures were taken on two dogs five times daily; i.e., 2:00 and 8:00 A.M., 12:00 noon, and 4:00 and 8:00 P.M. No elevation beyond the normal diurnal variation occurred following administration of beef blood cells and beef blood plasma. However, the dogs did appear to be sick and would lie listlessly in their cages. Their food consumption per day was somewhat diminished, but the fluid intake was usually increased after the administration of blood, cells, or plasma.

COMMENT

From the evaluation of our experiments on azotemia following intragastric administration of whole citrated beef blood, beef blood cells, and beef blood plasma, it would seem that blood in the gastrointestinal tract

undoubtedly causes an appreciable degree of azotemia. It would also seem that blood cells play the major role in producing azotemia, and that the degree of azotemia is directly proportional to the amount of blood, cells, or plasma put into the gastrointestinal tract.

Of the ingested materials used, i.e., whole blood, blood cells, and blood plasma, the average amount of hemoglobin in the whole blood was 11.65 Gm. per 100 c.c. as shown in Table I, and the average total plasma protein of blood was 4.74 Gm. per 100 c.c. Furthermore, the average hemoglobin content of blood cells was 29.36 Gm. per 100 c.c. as shown in Table I. These figures represent actual amounts of protein per 100 c.c. In other words, 29.36 Gm. hemoglobin per 100 c.c. for blood cells equals 29.36 Gm. of protein per 100 c.c. Hemoglobin is a protein containing iron and classified as a histone. These facts are suggestive that the azotemia was caused simply by the absorption of protein from the gastrointestinal tract with resultant urea formation in the liver from the absorbed protein. In these experiments, therefore, the chief cause of the increased blood urea nitrogen would not seem to be shock, hemorrhage, hypochloremia, decreased renal function, dehydration, increased body protein catabolism or shock, as shown in Table II.

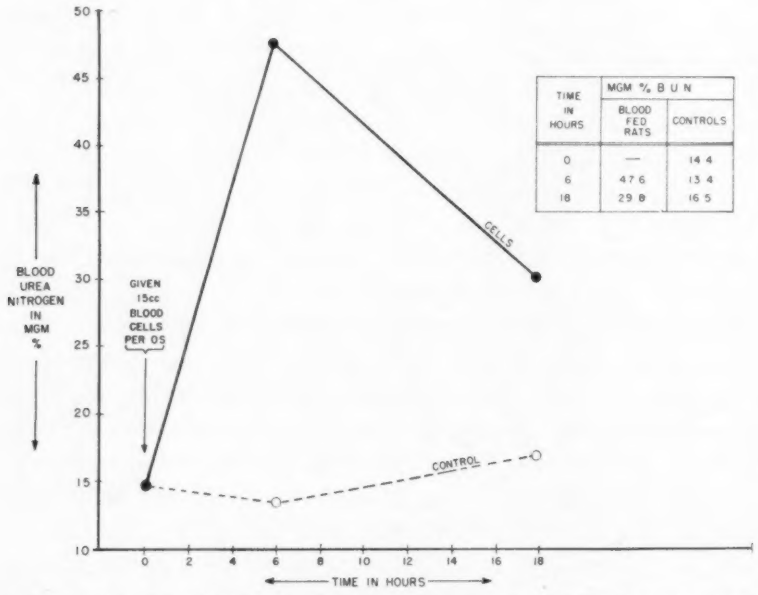


Fig. 2.—The effect of feeding red blood cells in the production of alimentary azotemia in the white rat.

Effect of Hemoglobin.—To carry this aspect of the investigation further, another experiment was performed using two dogs. One dog was given 60 Gm. of pure hemoglobin in two 30 Gm. doses four hours apart. The second dog received 100 Gm. of pure hemoglobin in one 60 Gm. and one 40 Gm. dose four hours apart. As is seen in Fig. 3, both dogs showed an initial increase in blood urea nitrogen in four hours, a

TABLE I

ANALYSIS OF SPECIMENS USED IN THESE EXPERIMENTS

SPECIMEN NO.	HEMOGLOBIN (GM. %)	HEMATOCRIT (%)	UREA NITROGEN (MG. %)	TOTAL PLASMA PROTEIN (GM. %)
		Whole Beef Blood		
1	11.0	33	19.1	4.3
2	12.6	35	9.9	5.0
3	13.0	37	17.7	5.2
4	10.0	36	16.1	4.5
5	–	–	16.9	–
Average	11.7	35	15.9	4.7
		Beef Red Cells		
1	28.5	–	19.1	–
2	28.4	–	10.7	–
3	31.2	–	13.9	–
Average	29.4	–	14.6	–
		Beef Plasma		
1	–	–	9.1	4.3
2	–	–	15.5	5.0
3	–	–	14.4	5.2
4	–	–	–	4.5
Average	–	–	13.0	4.7

maximum concentration of blood urea nitrogen in twelve hours, and a return to normal in twenty-eight hours. Furthermore, the dog receiving the larger dose of hemoglobin showed consistently higher blood urea nitrogen concentrations, leading one to believe that the degree of azotemia was due to and directly proportional to the amount of ingested hemoglobin.

Effect of Protein.—Following this observation two dogs were given a single large protein meal consisting of casein and ground beef, the first dog receiving 83 Gm. of protein, and the second 175 Gm. The same type of azotemia curve was obtained as for whole blood, cells and hemoglobin. The initial elevation of blood urea nitrogen appeared in one hour with a maximum concentration in five hours and a return to normal in twenty-five hours. Here again as shown in Fig. 4, the curves parallel

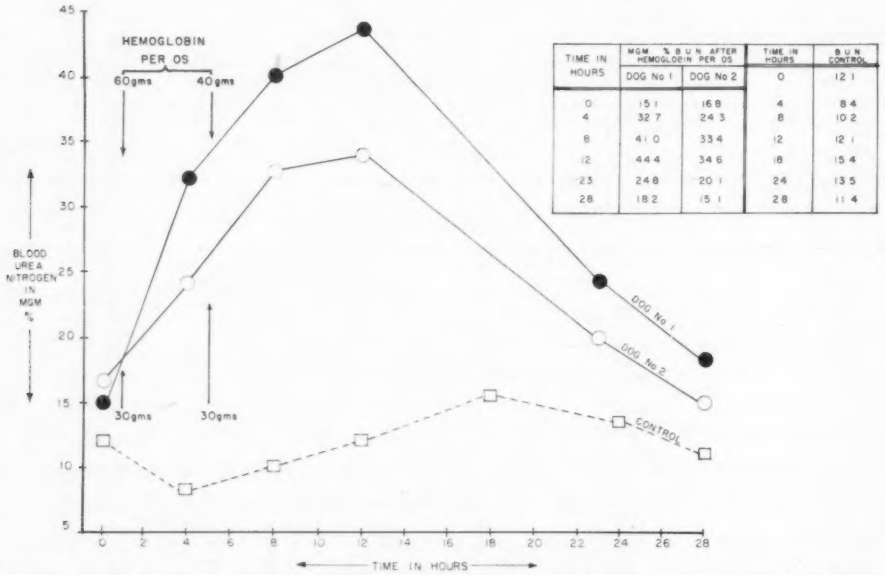
TABLE II

AZOTEMIA, POSSIBLE CAUSATIVE FACTORS AND CLASSIFICATION*

I. Renal
II. Extrarenal
  1. Shock
  2. Hemorrhage
  3. Hepatorenal
  4. Dehydration
  5. Starvation
  6. Increased body protein catabolism
  7. Hypochloremia
  8. Alimentary absorption

*Combinations may be frequent, thus shock may elevate the blood urea nitrogen by means of renal impairment, etc.

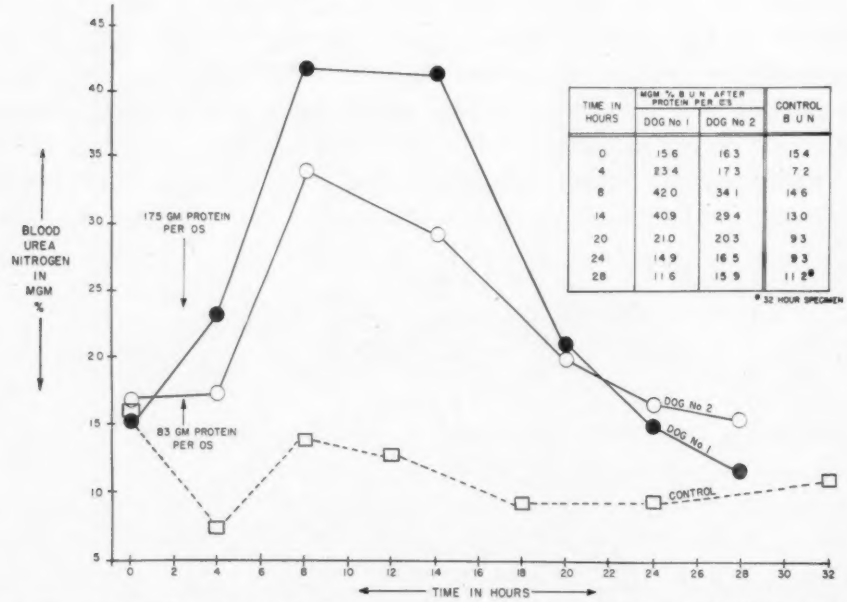
each other with the blood urea nitrogen curve of the dog receiving the larger dose of protein consistently several milligrams per cent above the other until normal is approached. That the protein in the cellular hemoglobin is the active element is corroborated by the results of Yuile and Hawkins[17] (1941). These authors have shown in an excellent presentation that the blood urea nitrogen rise following the injection of various substances is quantitatively proportional to their protein content.



TIME IN HOURS	MGM % B U N AFTER HEMOGLOBIN PER OS	
	DOG No 1	DOG No 2
0	15 1	16 8
4	32 7	24 3
8	41 0	33 4
12	44 4	34 6
23	24 8	20 1
28	18 2	15 1

TIME IN HOURS	B U N CONTROL
0	12 1
4	8 4
8	10 2
12	12 1
18	15 4
24	13 5
28	11 4

Fig. 3.—The effect of hemoglobin in the production of alimentary azotemia in dogs.



TIME IN HOURS	MGM % B U N AFTER PROTEIN PER OS		CONTROL B U N
	DOG No 1	DOG No 2	
0	15 6	16 3	15 4
4	23 4	17 3	7 2
8	42 0	34 1	14 6
14	40 9	29 4	13 0
20	21 0	20 3	9 3
24	14 9	16 5	9 3
28	11 6	15 9	11 2*

* 32 HOUR SPECIMEN

Fig. 4.—The effect of protein in the production of alimentary azotemia in dogs.

Effect of Iron.—Two dogs were given approximately 1 Gm. of iron each by stomach tube in the form of 10 per cent iron ammonium citrate solution. The blood urea nitrogen curves were quite flat one and two days later, showing no azotemia following administration of rather large doses of iron (1 Gm. of iron is the amount normally present in 1,000 c.c. of human blood[11]).

Effect of Urea.—It is well known that urea given by mouth will increase the blood urea content. The possibility arises therefore that the urea contained in red blood cells might explain their greater effect in production of alimentary azotemia as compared to plasma. Comparison of the figures represented in Table I readily dispels this idea. It is seen that the average urea nitrogen content of beef plasma is 13 mg. per cent, while that of beef red cells is only 14.6 mg. per cent, an inappreciable difference.

SUMMARY

The intragastric administration of citrated beef blood cells in five experiments revealed an initial elevation of blood urea nitrogen within four hours and a maximum concentration between five and twelve hours (depending on the amount and number of doses given) with a return to normal in twelve to seventeen hours following the last administration of cells.

Five dogs were given varying amounts of beef plasma into the stomach. Four of these revealed an initial elevation of blood urea nitrogen between four and eleven hours, a maximum concentration between eight and eleven hours (depending on the amount and number of doses given) with return to normal levels in five and one-half to twenty hours following the last administration of plasma. One dog revealed no elevation above normal. The average degree of azotemia attained for plasma-fed dogs was much less than that of the cell-fed dogs.

A comparable curve was obtained in white rats following administration of blood cells into the stomach.

Two dogs were fed 60 and 100 Gm. of pure hemoglobin respectively. Both showed an initial elevation of blood urea nitrogen in four hours, a maximum elevation in twelve hours, and a return to normal in twenty-eight hours.

Two dogs were fed large protein meals and showed an initial elevation of blood urea nitrogen in one hour, a maximum concentration in five hours, and a return to normal in twenty-five hours.

Blood urea nitrogen values were not elevated in two dogs given 1 Gm. of iron (10 per cent iron ammonium citrate) each by stomach tube.

Analysis of the blood cells and blood plasma used indicated that the greater activity of cells in comparison to plasma in producing a rise of blood urea nitrogen could not be explained by an excess of urea inherent in the cells.

CONCLUSIONS

1. Alimentary azotemia seems to be due to the red cell element of blood to a greater degree than to the plasma fraction.

2. Since marked rises in blood urea nitrogen were also obtained following ingestion of hemoglobin and protein, the rise caused by ingested blood probably is due to and to a large extent proportional to the resultant absorption of protein from the gastrointestinal tract.

3. The ingestion of iron in large amounts was found not to produce alimentary azotemia.

REFERENCES

1. Chunn, C. F., and Harkins, H. N.: Experimental Studies on Alimentary Azotemia. I. The Role of Blood Absorption From the Gastrointestinal Tract, SURGERY **9**: 695-705, 1941.
2. Chunn, C. F., and Harkins, H. N.: Alimentary Azotemia Due to Whole Blood Absorption From the Gastrointestinal Tract, Proc. Soc. Exper. Biol. & Med. **45**: 569-571, 1940.
3. Chunn, C. F., and Harkins, H. N.: Alimentary Azotemia: A Clinical Syndrome Occurring as a Part of the Bleeding Peptic Ulcer Complex, Am. J. M. Sc. **201**: 745-749, 1941.
4. Schiff, L., Stevens, R. J., Goodman, S., Garber, E., and Lublin, A.: Observations on the Oral Administration of Citrated Blood in Man. I. The Effects on the Blood Urea Nitrogen, Am. J. Digest. Dis. **6**: 597-602, 1939.
5. Kaump, D. H., and Parsons, J. C.: Extrarenal Azotemia in Gastro-Intestinal Hemorrhage. II. Experimental Observations, Am. J. Digest Dis. **7**: 191-194, 1940.
6. Chunn, C. F.: Azotemia Following Intragastric Administration of Blood: Studies on Experimental Animals, Thesis, University of Michigan, May, 1940.
7. Harkins, H. N.: Discussion of paper by Schiff, L.: Meeting of the American Medical Association, New York, June, 1940, Am. J. Digest. Dis. In press.
8. Boals, R. T., Chunn, C. F., and Harkins, H. N.: Alimentary Azotemia: A Part of the Bleeding Peptic Ulcer Complex. Clinical and Experimental Studies, Program Meeting Cent. Soc. Clin. Research **13**: 26, 1940.
9. Yuile, C. L., and Hawkins, W. B.: Azotemia Due to Ingestion of Blood Proteins: Blood Urea Increase Related to Ingestion of Whole Blood Red Cells, Plasma and Other Proteins, Am. J. Sc. **201**: 162-167, 1941.
10. Van Slyke, D. D., and Cullen, G. E.: In Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, 1932, Williams and Wilkins Co., vol. 2, p. 547.
11. Mathews, A. P.: Physiological Chemistry, New York, 1924, William Wood & Co.

REPAIR OF THE LARGE UMBILICAL HERNIA

ELLIOTT MICHELSON, M.D., AND WILLIAM RAFFEL, M.D., BALTIMORE, MD.
(From the Surgical Service of Sinai Hospital)

THE surgical treatment of the umbilical hernia depends upon its size. The umbilical hernia possessing a small sac is usually found in the young and thin, is surrounded by excellent fascia and offers no problems to the operator since it can be easily repaired by any number of simple methods with excellent end results. We are concerned in this paper with the large umbilical hernia which occurs in older and obese people, has relatively poor contiguous fascial structures, and is apt to recur in over 10 per cent of the cases when the best type of operation is performed.

The small umbilical hernia was adequately controlled even before the time of Celsus by reduction and simple forms of trussing. The larger types were always difficult to reduce and even less amenable to binding until Lucas-Championnière in 1881[1] successfully executed the open operation by overlapping the lateral edges of the rectus fascia. Eighteen years later William J. Mayo[2] suggested the transverse overlapping of the fascial flaps and this procedure is today recognized as most satisfactory. The incidence of over 10 per cent recurrence[3] using the Mayo technique has led us to develop a modification which obviates certain known faults.

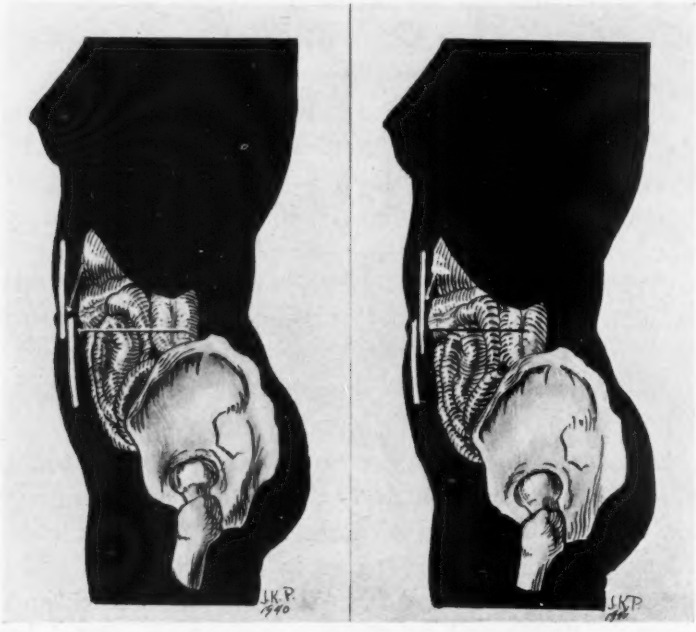
The umbilical hernia starts as an outpouching through the weak area at the upper angle of the umbilicus at the site of the obliterated omphalomesenteric vein. The vectors of force at this point are outward and downward and as the pouch increases in size, the bowel and omentum insinuate through the neck and push the lateral edges of the recti outward. Since in the large hernia the rectus muscle cannot be brought to the midline, the repair can only make use of the contiguous fascia. The transverse overlapping is recognized as an excellent procedure in strengthening the fascial closure, but what has not been suggested in the past is the possibility that the abdominal contents following the vectors of force may be insinuated between the flaps if the method of Mayo is used. We have imbricated our flaps in a manner exactly opposite that of the Mayo method by placing the upper flap posterior to the lower flap as seen in Fig. 1. The second weak spot in the Mayo repair is at the lateral angle. When one imbricates two straight fascial edges, one finds that either the lateral angles are not overlapped or an oblique tunnel is formed at either angle. This fault was recognized by Stone[4] and corrected by a method of plication which, however, did not overlap the

Received for publication, March 23, 1941.

first fascial layer. By curving the lateral angles upward we have produced a convex upper flap and a concave lower flap that permit overlapping at all points, prevent tunnel formation at the angles, and do not introduce further weakening areas of the wall.

OPERATION

A transverse elliptical incision is made about the umbilicus extending through the skin and subcutaneous tissue to the aponeurosis of the rectus. The fascia is then cleaned for a distance about the neck of the sac and the sac entered. With a finger in the peritoneal cavity, the sac is completely excised together with overlying skin. The contents of the sac are reduced and repair follows. If the neck of the sac has not been enlarged during taxis of the hernial contents, it is now done, the incision being



A. *B.*

Fig. 1.—*A.* In the Mayo umbilical hernioplasty the vectors of intra-abdominal force (indicated by arrows) allow insinuation of contents between the fascial leaves. *B.* Modified technique shows lower fascial flap anterior to upper flap with no insinuation of intra-abdominal contents possible.

extended at the angles, cutting in an upward curve for a distance of 5 to 6 cm. This distance may be increased without weakening the wall. The flaps having been cleaned of fat and connective tissue, the upper flap is placed posterior to the lower flap and interrupted sutures of E silk inserted, the needle being passed through the lower flap from without inward, then through the upper flap in mattress fashion and back through the lower flap from within outward. (Fig. 2.) No attempt is made to close peritoneum separately, the suture traversing both rectus fascia and peritoneum. The sutures are placed at 2 cm. intervals and all are inserted before the knots are secured. The overlapping or re-

dundant edge of the lower fascial flap is then sutured to the upper rectus fascia with interrupted E silk. No sutures are placed in the subcutaneous layer and the skin is closed with fine silk. In cases of marked obesity a small stab wound is made lateral and dependent to the incision and a rubber dam drain inserted.

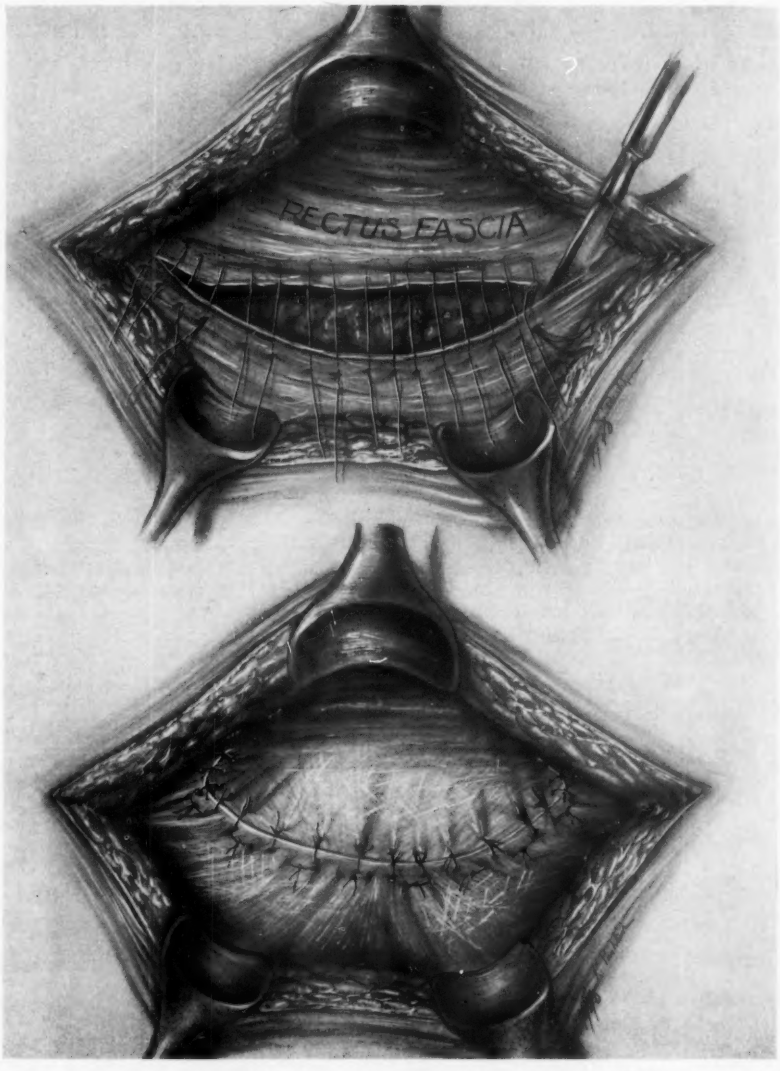


Fig. 2.—*A*. Sac has been removed and neck enlarged by extension of the incision in a curve upward at the angles. A convex upper flap and a concave lower flap are shown as result of this extension. Interrupted sutures are placed, bringing lower flap above upper flap. *B*. Repair completed by suturing redundant fascial flap to upper flap.

COMMENT

We suggest a modification of the Mayo operation because its use has been attended by a moderately high percentage of recurrences in the hands of skilled surgeons. There are two definite weaknesses in the Mayo repair which can be prevented. The first is responsible for re-

currences at the central portion of the incision and is due to insinuation of abdominal contents between the imbricated fascial leaves. The second weak area is at the lateral angle and is due to overlapping of straight fascial edges. The operation described above strengthens the central weak area, prevents insinuation of abdominal contents through the fascial leaves, overcomes the weak imbrication at the angles, and prevents tunnel formation. It can be used in all types of umbilical hernias but is recommended only for the large adult cases since the small hernia can be cured with less radical surgery.

CONCLUSIONS

Modification of the Mayo operation for large umbilical hernia is suggested.

Recurrences at the central portion of the repair are probably due to insinuated contents through fascial layers and are here obviated by placing the lower flap anterior to the upper flap.

Recurrences at the lateral angles may be due to faulty imbrication of straight fascial edges and are here remedied by using curved fascial flaps.

REFERENCES

1. Lucas-Championnière, J.: La hernie ombilicalie, J. de med. et chir. **66**: 609, 1895.
2. Mayo, William J.: Radical Cure of Umbilical Hernia, Ann. Surg. **34**: 276, 1899.
3. Simmons, C. D.: The End-Results of 70 Consecutive Cases of Umbilical Hernia Operated Upon at the Massachusetts General Hospital, Boston M. & S. J. **174**: 342, 1916.
4. Stone, Harvey: Umbilical Hernia—A Method of Operative Treatment, Arch. Surg. **12**: 494, 1926.

Editorial

A "New" Polio Treatment

ONCE AGAIN the popular press has grasped a spectacular piece of medical news and greatly distorted it. The saga of Sister Kenny of Australia and her polio cure, which was first discussed in medical journals in 1938, has now reached the Hearst *American Weekly* (Aug. 17, 1941) where medical men are characteristically flayed for their needless conservatism and inordinate ignorance. Her empiric methods of hot packs and muscle training are described as likely to revolutionize the treatment of poliomyelitis and to effect cures in more than half the cases treated.

Careful statistical studies of Sister Kenny's methods have been undertaken by Wallace Cole and his associates at the University of Minnesota, and from these it can be determined whether this "abandonment of immobilization" is of any real value or not.[1] Nevertheless until the Minneapolis investigators submit their final report this entire question must remain unsettled.

That others devised similar therapeutic methods long ago is well illustrated in a forthcoming history of medicine in Texas,[2] wherein Elena Zamora of south Texas describes her father's cure:

"When a young boy (in the 1850's) Porfirio Zamora and other members of the little settlement along the Rio Grande were stricken with 'El Tullidor,' the crippler, as they called it. My father survived, but was left with arms and legs entirely paralyzed. He had no strength in his neck to keep him erect so he had to lie in bed all the time. One day an Indian from the Tolcha tribes, around what is now Laredo, told my mother that one of the Indian chiefs of that tribe could cure victims of 'El Tullidor.' Grandmother knew it was a long and tedious journey to Las Lajas, the Indian encampment there. Preparations were made and the cavalcade departed. They went in ox carts escorted by men on horseback. When they arrived at Las Lajas they were given a large cabin by the Chief, Juan Castro. He told Grandmother that he was going to try to cure her son . . . and that he was to have entire control of the boy. Grandmother was willing to do anything that would restore her son to normalcy.

"A trough long enough for father to rest in comfortably was built at the chief's orders. Then the cure began. Each morning he was taken to the sands and allowed to lie there while two men, who took charge of him, rolled him over the hot sands and covered him with them. He

was then taken into the cabin and dipped into the trough filled with goat's milk. This milk was kept as hot as it was possible, by drawing off quantities of it and replacing them with hot milk. All the time he was in the milk trough he was being massaged and his joints moved constantly. This treatment lasted for almost an hour. He was then bathed in warm clean water and put to bed. . . . He was left alone till late in the evening when he was again massaged, but this time it was with a salve made from goat marrow and pungent herb. . . . At bed time he was given another treatment. Every joint in his body was covered with a poultice made from ground corn, goat milk, and oil from the marrow of bones. These poultices were kept warm by dropping warm oil on the covers. He slept with these bandages on. The treatment continued for many days. He felt as if his whole skin was raw, but not uncomfortable. Every night before being left with Grandmother for the night he was given . . . a tea brewed from herbs and a small quantity of Mescal.

"One night father awoke and felt a very pronounced desire to scratch a certain place on his neck. . . . Suddenly his fingers moved, he tried to raise his hand and it responded, and slowly but surely, he reached the itchy spot on his neck and scratched it to his heart's content. . . . He tried the other hand, it moved also, but not as freely. He turned his neck and it responded. He wriggled his toes, moved his legs, and then he began to cry, returning thanks to God and the Old Indian. . . .

"It was not long before he was able to sit up, then stand and practice a few steps. All the while the treatments continued. At last he was well, his limbs began to fill out, he could walk for several minutes without aid. The miracle had been performed. . . ."

Thus old Chief Juan Castro living in the lower Rio Grande Valley 100 years ago anticipated the routine devised by Sister Kenny in the Australian Bush, and as the record shows cured at least one patient. Perhaps if physiotherapy methods in poliomyelitis are to be profoundly altered and our concepts of treatment revolutionized, the new therapy should properly be called the Juan Castro-Sister Kenny treatment for poliomyelitis.

REFERENCES

1. J. A. M. A. **116**: 2577, 1941; Time, June 23, 1941.
2. Nixon, P. I.: History of Medicine in Texas. Unpublished manuscript.

—*Walter G. Stuck, M.D.*
San Antonio, Tex.

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

RECENT PROGRESS IN THE SURGICAL TREATMENT OF LUNG TUMORS

W. E. ADAMS, M.D., CHICAGO, ILL.
(From the Department of Surgery of the University of Chicago)
(Continued from the November issue)

TREATMENT

Until within recent years, surgical extirpation of lung tissue for carcinoma was attended by so great a risk that most lung tumors were treated either by bronchoscopic removal or by deep x-ray. After years of investigation, treating hundreds of patients by this method, it has become generally believed and more recently quite definitely proved that bronchogenic carcinoma has not been cured by x-ray therapy.[23, 53] In a recent communication Steiner[54] reports the results of x-ray treatment and its histologic effects on both the primary growth and the metastatic lesions. In no patient was a cure effected and survival was not noticeably prolonged by the irradiation.

Surgical treatment has been carried out sporadically for several decades. In 1912 a monograph on the subject was published by Adler,[55] who states: "There is every reason to hope that the technique of this new branch of surgery will be still further developed and that in the near future thoracotomy and operations on the lungs will be attended by no more risk than peritoneal operations today. If this is so, a new and great responsibility is placed upon the shoulders of internal medicine. It will be necessary, not only to educate the opinion of the laity so as to induce them to submit to these operations with the same readiness with which they now submit to peritoneal operations, but it will also be the sacred duty of the physician to recognize these cases and to recognize them as early as possible. When all the means of diagnosis outlined in this little study fail, where there is suspicion of tumor, but no assurance is possible, there should be—it is emphatically here stated—as little hesitation is resorting to an exploratory thoracotomy as there is now in submitting to an exploratory laparotomy." Adler's prediction has in substance come true and when his suggestions are followed beneficial results from surgery can be expected.

Anesthesia.—As has been previously stated, alteration of intrathoracic pressures with its deleterious effects on cardiorespiratory function has

been an important factor in the delay of progress made in intrathoracic surgery in general. Anesthesia is naturally very closely associated with the problem of preventing these deleterious effects. The maintenance of sufficient lung function during a surgical pneumothorax is of paramount importance to the success of the operation. The principle of the negative pressure chamber, as well as that of the positive pressure anesthesia technique originally administered by means of an intratracheal catheter has been applied to overcome this hazard. Intratracheal positive pressure anesthesia has enjoyed much success in performing this function. "Controlled respiration" without voluntary respiratory effort on the part of the patient may be obtained by the

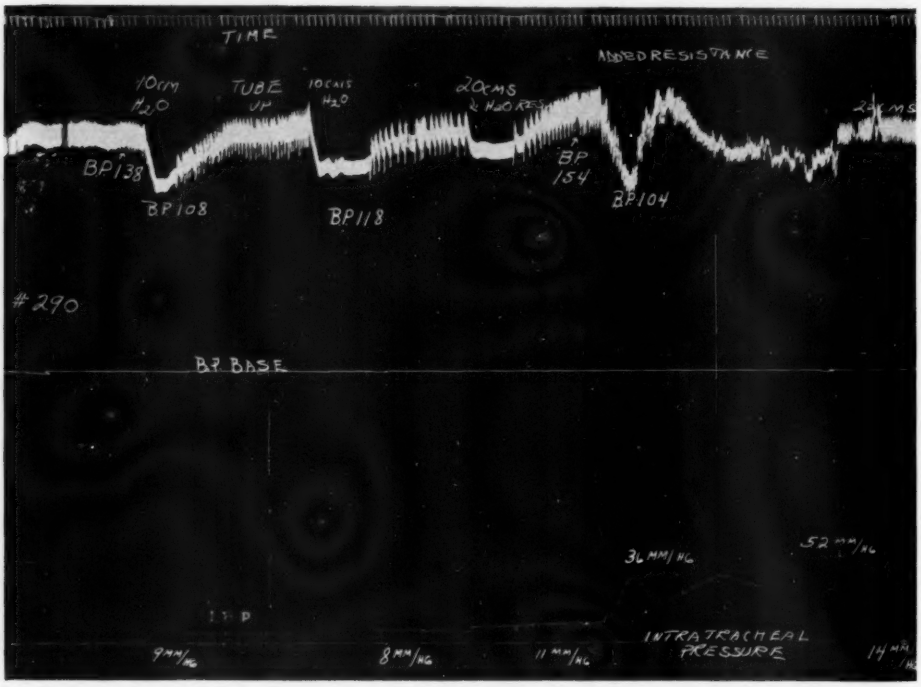


Fig. 7.—Kymographic tracing showing the fall in systemic blood pressure with periods of apnea due to increased continuous intrabronchial pressure from 8 to 52 mm. Hg. Some degree of transitory overcompensation on release of pressure is noted in both blood pressure level and respiratory activity. (*B. P.* Blood pressure. *I. B. P.* Intrabronchial pressure.)

use of the proper mixtures of anesthetic agents administered under certain pressures. It also prevents suffocation by spasm of the glottis and, furthermore, allows for the aspiration of mucus and pus from the tracheobronchial tree, both during and at the termination of surgery. Because of its obvious usefulness, intratracheal positive pressure anesthesia has been widely accepted, and without sufficient attention being given to possible hazards or disadvantages. That these are present and may lead to disastrous results is evidenced by the reports of Stephens,[56] Bradshaw,[57] Bourne,[58] and Heidrick and co-workers.[59]

Elsberg[11] is usually credited with having performed the first thoracic operation using intratracheal insufflation anesthesia and in 1911 reported more than one hundred cases with very satisfactory results.

Little investigative work has been reported on the deleterious effects of positive intrabronchial pressure on the cardiorespiratory function in general, and on the parenchyma of the lung in particular. Macklin[60, 61] produced mediastinal emphysema and pneumothorax following overdistention of an isolated portion of the lung in cats. He demonstrated interstitial emphysema about the vascular tree of the lung with air progressing toward the hilum and into the mediastinum, and reasoned that the pneumothorax was secondary to the emphysema. Pressures employed in his studies varied from 10 to 200 mm. of mercury. His findings were substantiated by Marcotte and his associates[62] in our laboratory, the intrabronchial pressures necessary for the production of mediastinal emphysema being determined. A study of the alteration of the arterial blood pressure was also made at the same time. Briefly, it was found that in the dog a routine fall in the systemic arterial blood pressure of 8 to 10 mm. of mercury resulted from an elevation in intrabronchial pressure of 6 mm. of mercury. Intrabronchial pressures of 24 mm. of mercury or above were routinely accompanied by the development of mediastinal emphysema. The latter effect was produced in cats with only 20 mm. of mercury.

That such deleterious effects occasionally occur from the clinical use of intratracheal positive pressure anesthesia is seen in reports by Bradshaw, Heidrick, and others as above stated. These findings do not necessarily indicate that positive pressure anesthesia should be abolished but that minimal pressures should be used and that one should be cognizant of such deleterious effects of high pressures.

That positive pressure anesthesia is not always a prerequisite for intrathoracic surgery is demonstrated by the use of spinal anesthesia, a method which has been extensively employed with satisfactory results by surgeons both in Canada and England. T. Edwards[16] reported the use of percaine (1:1,500) with consistent anesthesia up to the level of the third dorsal segment maintained for well over two hours. He stated that the "advantages of cutting off nerve impulses arising from separation of dense adhesions between lung and chest wall and thereby limiting shock are obvious and although it is common to see a preliminary fall in blood pressure due to the anesthetic to rise during the later stages of the operation, when the operative effects should be appearing." When spinal anesthesia is used and cough produces respiratory distress, damage is "controlled by the administration of a little oxygen given under light positive pressure, with a firm-fitting face piece."

In the United States, surgeons have usually preferred general anesthesia using cyclopropane or ethylene-oxygen mixtures. Although intratracheal catheter administration has been widely employed, an ever-increasing number of surgeons have discontinued its use because of the

likelihood of introduction of infectious material from the mouth into the lower respiratory air passages or of injuring the mucous membrane of the tracheobronchial tree with subsequent inflammatory changes.[47, 64-66] We have found ethylene-oxygen administered through a snug-fitting face piece a very satisfactory anesthesia for various types of intrathoracic operations.

In conclusion, one may say that the simplest type of anesthesia, unhindered by complicating apparatus or traumatizing procedures in which minimal positive pressure is possible, is the anesthetic of choice. The method should facilitate good exposure, provide adequate oxygenation and support to respiration, necessitate minimal motion of the lungs with least interference of cardiorespiratory function, be nonirritating to the respiratory passages and minimize postoperative complications.

PREOPERATIVE PREPARATION

Preoperative preparation should include both local and general measures that best fit the patient for the alteration in cardiorespiratory function both during and following the surgical procedure. Not infrequently, a blood transfusion is necessary because of the existing anemia. Cross-matching for further transfusion either during or possibly following operation is also an essential procedure. Careful check-up of the cardiovascular system will lower the incidence of postoperative shock and cardiac failure. The question of preoperative digitalization as yet has been unsettled but may prove of definite value in certain individuals.

Where the necessity of total pneumonectomy is obvious, preliminary pneumothorax has several advantages. It not only gives information regarding the presence of adhesions between the lung and chest wall, as well as some of the characteristics of the existing tumor, but prepares the patient for cardiorespiratory function using only one lung following the operative procedure. By reducing the lung function slowly over a period of several days, the shock is thought to be much less severe than when the procedure is accomplished suddenly during the operation. The reduction in size of the lung to be removed is also of some advantage at the time of operation.

Rienhoff[67] has advised the use of beef broth for the production of granulations lining the pleural space prior to operation. This is accomplished by the use of 50 c.c. of beef broth bouillon introduced into the pleural cavity following the induction of pneumothorax. An effusion is produced which increases for approximately two days with polymorphonuclear leucocytes predominating. Within five to seven days the predominant cell is changed as the lymphocytes increase. The object of this procedure is to prepare a defensive wall against infection of the pleural space following surgery. This procedure as yet has not been widely used but may have value where few or no adhesions exist between the lung and chest wall.

THE QUESTION OF OPERABILITY

Contraindications to operation may be directed toward the general condition of the patient or to local or metastatic involvement by the tumor. If the cardiovascular system is obviously markedly below par or if other degenerative changes have produced considerable debilitation, it is obviously unwise to subject the patient to such a major operation as pneumonectomy. Since the mortality of bronchogenic carcinoma has been practically 100 per cent without surgical intervention, many patients have been treated by resection of the involved lung where little hope was entertained for a permanent cure. With increasing experience, however, many of these hopeless conditions became obvious when exploratory laparotomy was performed, thus helping to prevent the operation from falling into disrepute.

As in the case of malignant tumors elsewhere in the body, obvious metastases contraindicate surgical intervention. When signs, symptoms, and diagnostic methods reveal no evidence of metastatic involvement, an exploratory thoracotomy is indicated. Considerable discussion regarding the presence of mediastinal glandular involvement as being a contraindication to surgery has not led to a universal agreement. It is known however that tumor-bearing lymph nodes may be removed together with the involved lung and the patient remain healthy and active without evidence of recurrence or metastatic involvement for some time.[68*] This question will probably be better answered as more experience is gained in the handling of the tumor.

OPERATION

The earlier operations performed for primary lung tumors consisted chiefly of the removal of one lung lobe or a portion of a lobe. Subsequent observations revealed that recurrence of the tumor or continuation of growth of the metastases was apt to result in a high percentage of patients where this was carried out. The operation of choice, therefore, was found to be a total pneumonectomy with resection of the mediastinal lymph nodes. More recently, a two-stage pneumonectomy has been devised and carried out by Rienhoff[69] in this country and by Edwards[70] in England. This procedure has been reserved more especially for older or poor-risk patients in whom the one-stage operation is too dangerous. In performing a total pneumonectomy, careful dissection of the vessels and bronchus at the hilum with individual ligation of the former is the procedure of choice. This enables a higher division of the primary bronchus and an adequate exposure for removal of mediastinal lymph nodes. Thus, by resection of an adequate amount of the tumor-bearing tissue at its primary site and the regional lymph nodes which are the first to be involved by metastases, a much higher percentage of permanent cures may be expected.

*Patient reported is living and well four and one-half years following operation.

That there remains an indication for lobectomy in the treatment of a small percentage of slow-growing bronchogenic carcinomas is a view held by a number of authors.[42] This group of tumors originates in the primary stem bronchi, and they are very slow to invade adjacent structures or to metastasize. Since the risk of pneumonectomy still remains considerably higher than that of lobectomy, if the latter operation is adequate to remove all tumor-bearing tissue, it is thought to be the procedure of choice in these patients.

Approach.—Three main sites for approaching these operations have received considerable attention; namely, anterolateral, posterolateral, and lateral. The anterolateral approach which enters the pleural space

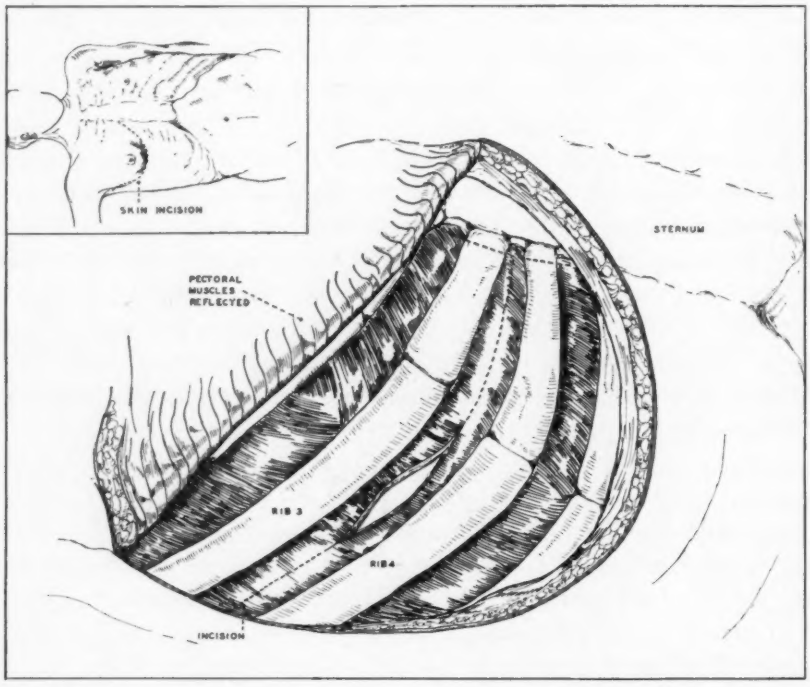


Fig. 8.—The anterolateral approach, showing the line of incision beneath the breast. With the pectoral muscles divided and elevated upward the pleural space is entered through the third intercostal space. The third and fourth costal cartilages may be divided near the sternum.

through the third or fourth interspace from the lateral border of the sternum to the postaxillary line received earlier attention for total pneumonectomy. The incision may be made either along the crease beneath the breast (especially in women) or just over the nipple along the line of the interspace, and the procedure may or may not include the division of the second, third, fourth, and fifth costal cartilages. Graham[71] and Overholt[72] have been strong advocates of this latter procedure; whereas, Rienhoff[73] approaches through the third interspace without the division of ribs or cartilages. The anterolateral approach is especially applicable for pneumonectomy because of its adequate exposure of the anterior aspect of the hilum for a detailed dissection of its structures. It also

gives visibility for the division of adhesions in the anterior and superior aspects of the pleural space which are apt to be present in the case of carcinoma of the upper and middle lobes. This approach has been used for many years by Graham and T. Edwards and others for the removal of anterior mediastinal tumors, and if the incision lies beneath the breast in women, it may leave little evidence of scar following healing and little or no deformity visible on x-ray examination.

The posterolateral approach is made through an incision along the course of the seventh rib from its angle posteriorly to the anterior axillary line and may include the resection of a long segment of this rib subperiosteally with or without the division of the fourth, fifth, sixth, and eighth ribs posteriorly. This approach is used more especially for

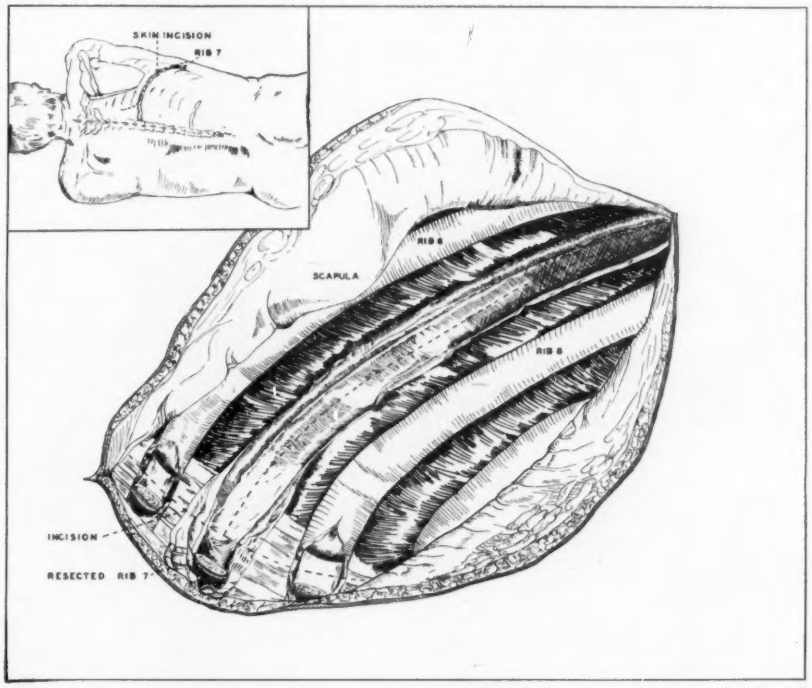


Fig. 9.—The posterolateral approach. The incision is made along the course of the seventh rib, extending upward near the spine posteriorly. The pleural space is entered through the seventh rib bed. Small segments of the sixth and eighth ribs posteriorly have been removed.

lobectomy, rather than for pneumonectomy, and has the advantage of permitting better visibility for the division of adhesions posteriorly and inferiorly between the lower lung lobe and the diaphragm. Since infection subsequent to obstruction of the bronchial tree by the tumor is present in a high percentage of cases, pneumonitis and bronchiectasis with subsequent inflammatory reaction between visceral and parietal pleurae with the production of adhesions are common complications. The disadvantage of this approach for pneumonectomy lies in an inadequate exposure of the anterior aspect of the hilum, a factor of great importance in the dissection of the hilar structures in the resection of the lung.

More recently, a lateral approach has been devised and utilized by Crafoord,[74] of Stockholm, and at the present time is receiving ever-increasing favor in other parts of the world. This approach utilizes an incision along the course of the fifth rib, extending from the fourth rib at its angle posteriorly, downward and forward to the costochondral junction of the fifth anteriorly and dipping beneath the scapula on its way forward. After division of the muscles of the chest wall and elevation of the scapula almost the entire length of the fifth rib is removed subperiosteally. This approach combines all of the advantages of the two former approaches, thus the explanation for its increasing favor. It allows for more adequate exploration under direct vision and facilitates materially the removal of the involved structures.

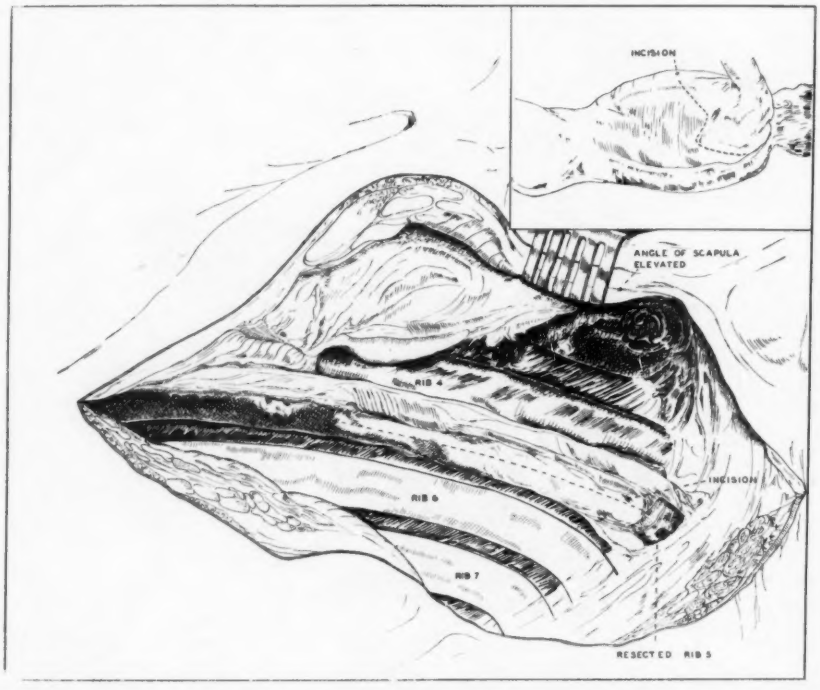


Fig. 104.—The lateral approach. Insert shows the skin incision over the course of the fifth rib anteriorly and curving beneath the scapula posteriorly. After elevation of the scapula most of the fifth rib is resected and the pleural space entered through this rib bed.

Before making the incision for entering the chest, intravenous saline administration is begun and continued at a slow rate throughout the operation. If exploration reveals the tumor to be operable, blood for transfusion is substituted for the saline solution and administered at a slow rate during the lung resection. During the entire procedure, blood pressure and pulse recordings are made at five-minute intervals and the surgeon is informed if any severe alteration occurs.

On entering the pleural cavity, examination of the tumor is immediately carried out to ascertain operability. The degree of fixation to the mediastinum is of importance in determining this factor. Mediasti-

nal lymph nodes may be enlarged due to infection complicating the primary condition. Adhesions are divided and oozing of blood is controlled by direct application of warm, moist sponges. As previously mentioned, where adhesions are dense and extend over a wide area, shock may be so severe as the result of their separation that the two-stage operation is indicated. This consists of the mobilization of the pulmonary artery and its division between ligatures. The wound is then closed and the lung removed at a second stage. Where few dense adhesions are present and little shock is observed in their division, the one-stage operation is advisable and proceeds as follows: The diaphragm on the involved side is paralyzed by the division of the phrenic

Fig. 10*B*.—Photograph of patient showing healed incision of the lateral approach to the pleural cavity.

nerve between ligatures. This reduces the amount of motion in the lung to be removed and helps to reduce the residual space subsequent to surgery. Careful dissection of the hilar structures with mobilization of the main pulmonary artery and two pulmonary veins necessitates entering the mediastinal region, since that portion of the vessels lying outside of the mediastinum is too short for adequate ligation before division. Ligation of the vessels is best performed with nonabsorbable silk or linen sutures, rather than catgut, since the latter is more apt to slip, resulting in a fatal hemorrhage. The vessels are then divided

between ligatures, two of which have been placed proximal and one distal to the site of division. To insure permanent closure of the vessels a transfixion suture may be used for one of the two proximal ligatures. The mediastinum is then explored and all lymph nodes removed.

Reflex Effects During Operation.—Considerable emphasis has been placed by some authors on the deleterious effects during the dissection of the hilar structures, clamping of the bronchus, and ligation of the pulmonary artery due to reflex activity. It is well recognized that serious cardiorespiratory disturbances may result from reflex action due to stimulation of nerve endings in the parietal pleura, at the root of the lung, and in the mediastinum. The nerves over which these impulses must pass include the vagus, sympathetic, phrenic, and intercostal. This reflex action may be abolished by local anesthesia and may be increased by light general anesthesia. Morrison[77] produced sudden death in rabbits by crushing the pedicle with a clamp which produced an arrest of respiration in the inspiratory phase. This action could be prevented by first sectioning or injecting the vagus nerve proximally with novocain. Cardiac arrest was also produced by Nissin[78] and by O'Shaughnessy[63, 79] by clamping or ligating the hilum en masse in experimental animals. Dissection of the hilum may occasionally cause a slowing of the heart rate and lowering of the systemic blood pressure, the degree of which is of little consequence.[16] Temporary cardiac arrest has been reported due to this procedure, and pneumonectomy was prevented in one case when cardiac arrest resulted on attempts to clamp the pulmonary artery.[75] This is unusual, however, little change in blood pressure level or heart rate being the common observation. Animal experimentation carried out in monkeys and dogs by Monod[76] bears out the above clinical observations. Although inhibitory effects were noted, they were never sufficiently strong to produce cardiac arrest even with rough handling of the lung root or crushing the hilum en masse including the vagus nerve. Cocaine applied to the hilum before dissection has been advocated to avoid these reactions. I have never observed these untoward effects and from personal communications have been led to believe that they have been overemphasized.

Closure of Bronchial Stump.—Following the division of the pulmonary artery and veins, the primary bronchus is freed from the surrounding structures to a point not more than 2 cm. below the bifurcation of the trachea. The point of division of the bronchus will depend chiefly on the site of the tumor, a fact determined by bronchoscopy prior to operation. Cases have been reported in which even the lower part of the trachea has been resected for extremely high-lying tumors. Several methods for managing the bronchial stump have been advocated, but none has proved successful in 100 per cent of the cases. Leakage following closure of the stump has been one of the major causes of serious

postoperative complications. These complications include empyema, tension pneumothorax, pneumonia in the remaining lung, and sudden drowning of the remaining lung by fluid collected in the residual pleural space. These complications have given rise to the oft-repeated but as yet unanswered question as to whether thoracoplasty should be performed at the time of or following the pneumonectomy.

It was well established at an earlier date by Bettman,[24] and later substantiated in this laboratory,[25] that the healing power of the bronchus per se was peculiar in nature; thus when the bronchus was occluded by mass ligature following resection of an entire lung, reopening of the same could be predicted in a high percentage of animals. The explanation of this complication was chiefly on the basis of lack of healing in the bronchus per se when the lining mucosa remained intact. When the mucosa was destroyed by crushing of the bronchus or by cauterization prior to its obliteration by ligature or suture, reopening could be prevented in a high percentage of cases. Division of the bronchus in a biased direction and utilization of the musculofibrous portion for covering the end of the cartilaginous portion has been advocated by Rienhoff[80] as an additional safeguard against reopening. In young individuals, after closing the end of the bronchial stump by a row of interrupted sutures, inversion of the stump, as in treating the stump of an appendix, may be brought about by a series of interrupted mattress sutures. In older individuals, however, where the cartilages have become quite rigid, this is not possible. A more substantial closure in these cases must be obtained by the use of mattress sutures placed above the line of interrupted sutures closing the end of the bronchus as advocated by Overholt and others. Destruction of the bronchial mucosa by chemical cauterization has the advantage that raw surfaces of the bronchus are approximated by the mattress sutures and should give rise to more rapid solid healing. In closing the bronchial stump care should be taken not to disturb the bronchial artery since that portion of the bronchus distal to ligature or mattress sutures is partly nourished by this means. Following closure of the bronchus, burying the same in the mediastinum or covering it with a free lung parenchymal graft, as advocated by Churchill, may further enhance solid healing without subsequent reopening. This is a debated question, however, some prefering to leave it protruding into the pleural space.[81] Clean drapes are now placed about the wound, a change of gloves is made and a clean set of instruments used for closure of the wound. Protection of the wound edges by moist lap sponges during surgery will encourage healing by primary intention. Closure is made in layers, using a double strand of No. 0 chromic catgut for pericostal sutures placed around the ribs above and below the incision and a continuous suture of No. 00 chromic catgut for the intercostal structures. The muscles are carefully approximated with interrupted sutures of the latter material and closure completed without

drainage. After closure is complete, a needle introduced into the pleural space is attached to a pneumothorax apparatus to determine the residual pressures. Air is then aspirated until the pressures become within normal limits; i.e., minus 8 to 10 cm. of water. T. Edwards and Harrington have advocated drainage of this space following surgery for the removal of accumulated fluid and maintenance of pressure relationships. The drain is removed twenty-four to seventy-two hours later in order to avoid infection of the residual pleural space.

Postoperative Care.—The amount of blood lost during surgery and the degree of shock at the end of surgery determine whether a second blood transfusion is indicated. A higher percentage of successful results will be obtained where the free use of blood transfusions is employed when indicated. After the return of the patient to his room, oxygen is administered by a nasal catheter or by tent. If given by nasal catheter at the rate of 10 to 12 liters per minute, the amount may be sufficient for most patients. In the presence of a humid atmosphere or extreme elevation of temperature, oxygen given by the tent method is advisable. By either method, oxygen administration will diminish the strain on the cardiorespiratory system and reduce very definitely the incidence of cardiac failure. An apparatus readily available for the administration by mask of oxygen under pressure is advisable for occasionally its immediate use may be necessary.

Some authors, notably Rienhoff, have advocated the Trendelenburg position in bed for twenty-four hours following operation, maintaining that this permits free bronchial and tracheal drainage with minimal effort to the patient. Other surgeons favor the semisitting posture in which position cough and expectoration are somewhat facilitated. In either case, change of position from one side to the other or to the back every two or three hours while the patient is awake during the first two or three days is indicated. This helps to prevent the development of pneumonia in the remaining lung and tends to aid circulation. Administration subcutaneously or intravenously of 2,000 to 3,000 c.c. of saline solution or glucose daily during the first two or three days is indicated. A sudden rise in temperature to 101 or 102° with a somewhat rapid fall may be expected for the first two or three days. Some of this elevation is due to the absorption of blood from the pleural cavity and may persist for one or two weeks.

Examination of the chest by fluoroscopy or x-ray every two or three days is indicated in order to determine the condition of the residual pleural space and of the remaining lung as well as the position of the mediastinum. It is usually unwise to remove air or fluid from the residual pleural space to the point of creating high negative pressures. The air persisting there is gradually absorbed and replaced by fluid of a serosanguineous nature. When the pleural space is not prepared by the

use of beef broth prior to operation, the fluid found at this site following operation remains in a fluid state for at least several weeks or months following surgery.

Where healing of the wound occurs by primary intention, the patient may be able to sit out of bed by the end of two to three weeks and may be discharged from the hospital by the end of three or four weeks. If a

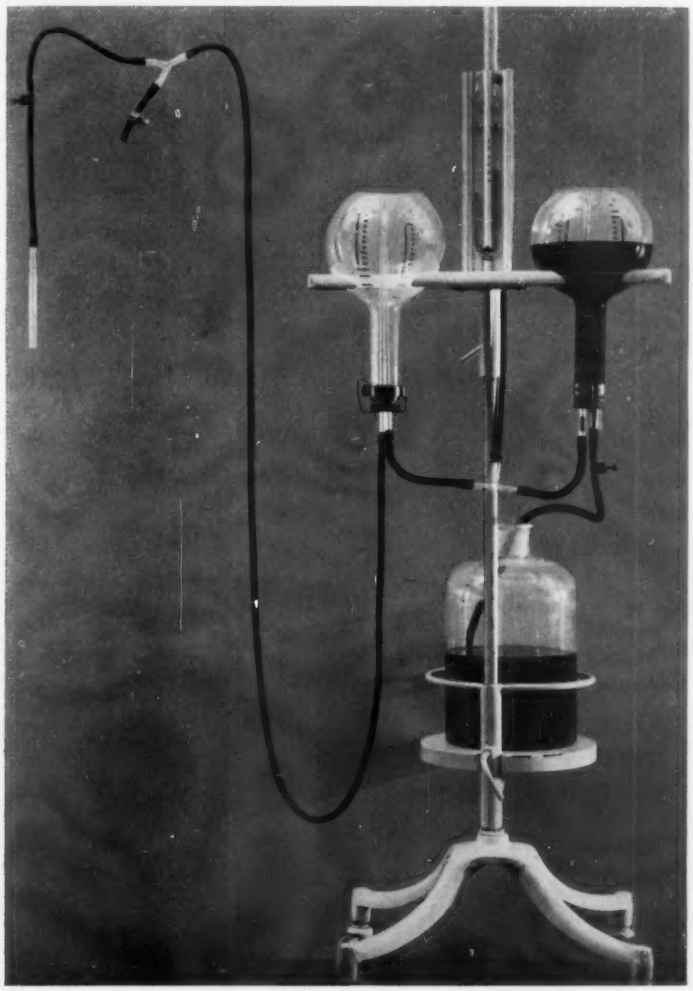


Fig. 11.—Modified double Wangensteen portable suction apparatus found to be satisfactory for draining and obliterating the pleural space following intrathoracic operations. A manometer connected with the tubing between the two upper flasks aids in determining the amount of suction applied to the pleural cavity.

cough develops or is persistent after operation, reopening of the bronchial stump with the production of a bronchial fistula must be suspected and is determined by bronchoscopic examination. In this event, an empyema of the residual pleural space must be expected and necessitates drainage of this space. Complete healing of the empyema may occur following adequate drainage with or without subsequent obliteration of the space by thoracoplasty.[16]

READJUSTMENTS FOLLOWING PNEUMONECTOMY

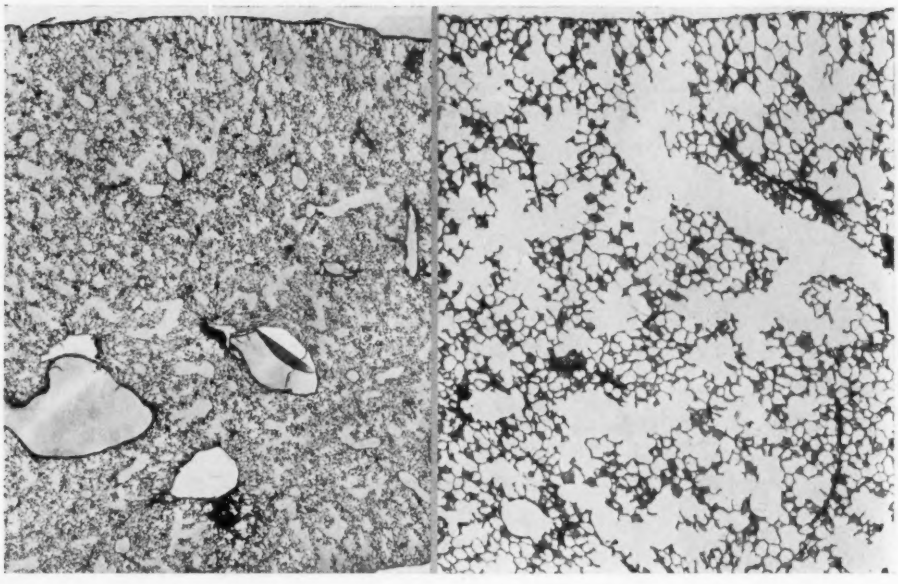
During the past eight years sufficient clinical material has been observed upon which definite conclusions can be based regarding the physical and physiologic alterations following pneumonectomy. Some of these may be observed within the first few hours after operation; viz., reduced respiratory movement on the side of surgery, with narrowing of the intercostal spaces, elevation of the diaphragm, and shifting of the mediastinum toward that side. These changes increase in degree during the subsequent few months and in addition there is a sinking of the pleural apex and a mild degree of scoliosis with the concavity toward the side on which the operation was made.

Residual Pleural Space.—Following the removal of an entire lung on one side the pleural space fills with a serosanguineous transudate and the air is gradually absorbed. It is usually unnecessary to remove air or fluid from this space following surgery provided a normal negative pressure is established after closure of the wound. As stated, some surgeons (Edwards,[16] Harrington[81]) prefer to drain this space for twenty-four to seventy-two hours in order to maintain a negative pressure. Rienhoff[83, 84] reports that the accumulating fluid coagulates within a few days, with the formation of many pockets in the meshes of a fibrous tissue network. In our experience this fluid remains uncoagulated for weeks or months[68] and becomes serofibrinous in character. The space is markedly reduced in size by elevation of the diaphragm, some shift of the mediastinum, contraction of the chest wall, and thickening of the parietal pleura. An autopsy performed on a 58-year-old man who died of general peritonitis nine months after total left pneumonectomy revealed 125 c.c. of serofibrinous exudate occupying a cone-shaped space made by a contracted parietal pleura which varied from 0.5 to 2 cm. in thickness.[85] The discrepancy between these findings and those of Rienhoff's report may well be explained by the preoperative preparation in his patients with beef broth which stimulates granulation tissue production.

In children, the mediastinum is able to shift more easily than in adults. Thus the lung on the uninvolved side actually herniates into and diminishes the size of the residual pleural space. This is also true in dogs and in addition little or no pleural fluid or parietal pleural thickening is found following pneumonectomy.[86]

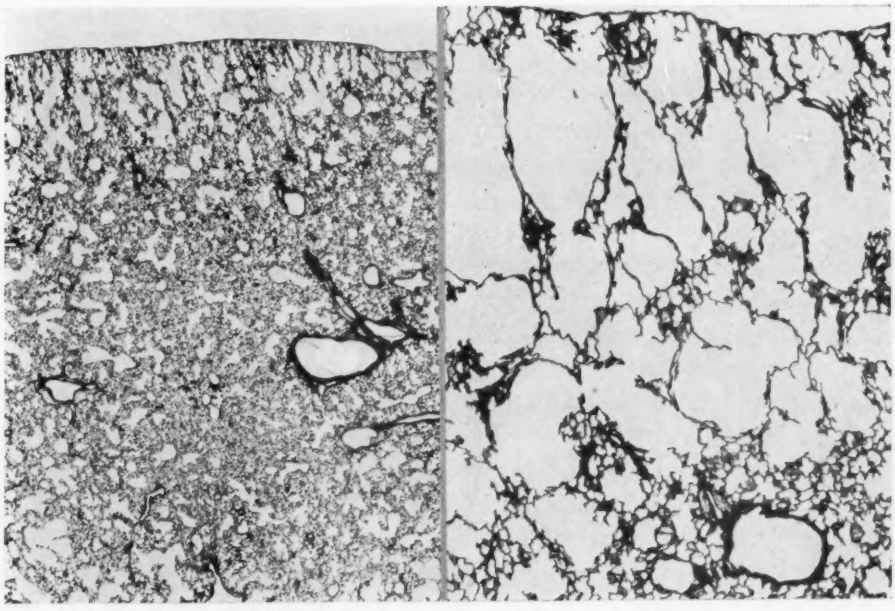
That the accumulation of fluid in the residual pleural space constitutes a real hazard is emphasized by the report of sudden death from asphyxia due to flooding of the remaining lung by sudden opening of the bronchial stump.[87] This is one factor that has given rise to the frequently debated but as yet unanswered question as to whether a thoracoplasty to obliterate this space should not accompany or follow the pneumonectomy.

The Remaining Lung.—Due mainly to the shift of the mediastinum and also to some extent to lowering of the diaphragm on the unin-



A. *B.*

Fig. 12.—Microscopic appearance of the lung following reduction of lung function to three lobes (38.7 per cent). Note uniform dilatation of the terminal respiratory units with no evidence of emphysema. (*A.* ×7. *B.* ×20.)



A. *B.*

Fig. 13.—Microscopic appearance of the remaining one upper lobe following the resection or collapse of the other five lobes (lung function remaining approximately 15 per cent). Note marked dilatation of the terminal respiratory units more especially near the surface of the pulmonary tissue. In some places emphysematous changes are demonstrable. (*A.* ×7. *B.* ×20.)

Complete report of case shown in Figs. 6 *A-D* to appear in SURGERY.

volved side,[84] the remaining lung fills a larger space following total pneumonectomy. Whether there is actual hypertrophy, hyperplasia, or true emphysematous changes has been a controversial subject. Rienhoff believes that neither of these occurs but that there is a simple overdistention of the pulmonary tissue, a view shared by most authors. This change is more marked following removal of the left lung since the right lung herniates into the left pleural space more easily than contrariwise. This is thought to be due chiefly to the anatomical arrangement of the mediastinal structures. Rienhoff has found similar alterations in both children and adults varying only in the degree of severity.

Considerable animal experimentation regarding the reduction of lung function has resulted in the following conclusions: If no more than one lung is removed in dogs and cats, only compensatory overdistention with no production of true emphysema of the lung occurs (Rienhoff, Reichert, and Heuer[88]). In rabbits some areas showed changes analogous to compensatory emphysema following total pneumonectomy (Morrison[77]). In rats (Hibber[89]) and in young cats (Longacre and Johansmann[90]) actual hyperplasia occurs following pneumonectomy. Behrend and Mann[91] however, believe the increased volume of the remaining lung is chiefly due to the use of functional units which are ordinarily inactive. Due to the extreme elasticity of lung tissue, Phillips and his associates[86] and Rasmussen and his co-workers[92] of this laboratory found it impossible to produce true emphysema until only one upper lobe or about 15 per cent of the lung tissue was functioning. The lobes revealed marked dilatation of the terminal respiratory units including the alveoli, air sacs, atria, and alveolar ducts, the overdistention being especially marked in the latter. There was some fragmentation of the walls of the alveolar ducts, but the alveoli for the most part were intact, with no destruction of elastic tissue and little disturbance of capillaries of pulmonary circulation. This latter is substantiated amply by both clinical and experimental evidence.

Cardiorespiratory Reserve.—Following pneumonectomy little or no cardiorespiratory embarrassment while at rest or under mild exercise occurs in an otherwise normal individual. The first patient to survive total pneumonectomy for carcinoma (performed by Graham), a doctor, is living and without symptoms more than eight years after surgery. He continues his surgical practice and during ordinary activities is unaware of signs or symptoms of embarrassment referable to the cardiorespiratory system. Many like examples of a shorter duration show this to be the rule rather than the exception. Much light has been shed on this aspect of the subject by animal experimentation. As early as 1922 Heuer and Andrus[93] observed a temporary rise in alveolar carbon dioxide and a fall in alveolar oxygen following pneumonectomy in dogs. With these changes there was an associated temporary rise in carbon-dioxide content and capacity of the blood with a marked

fall in the oxygen content and a marked decrease in the oxygen saturation. With this Andrus[94] found an increase of 40 per cent in blood flow through the opposite lung within a few hours after pneumonectomy. In other studies[95] he demonstrated an increase in respiratory volume, pulse rate, hemoglobin, and red cell count within twenty-four hours after ligation of the left main bronchus. All of the above alterations excepting the hemoglobin and oxygen capacity returned to normal within approximately one month.

Cardiorespiratory reserve following pneumonectomy was further studied by Longacre, Carter, and Quill[96] using induced exercises and anoxemic tests on young dogs before and at various periods following surgery. They found it to be sufficient to tolerate moderate exercise. According to their methods the reserve was reduced to 50 per cent by total pneumonectomy, but after four months this was raised to 66 per cent. The mechanism for this compensation could not be adequately explained.

TABLE I

RESULTS OF TEST FOR RESPIRATORY RESERVE AT REST IN NORMAL, 3-LOBE, 2-LOBE AND 1-LOBE DOGS BY REDUCTION OF ATMOSPHERIC PRESSURE IN EVACUATION CHAMBER (RESERVE OF 3-LOBE DOGS WAS SAME AS THAT FOR NORMAL ANIMALS WHILE THAT OF 1- AND 2-LOBE DOGS WAS SOMEWHAT REDUCED)*

STANDARD ATMOSPHERIC PRESSURE		CONDITION OF ANIMAL AND % OF FUNCTIONING LUNG	NO. OF DOG	ALTITUDE TOLERATED	TIME OF ASCENT (MIN.)	AVERAGES	
ALTITUDE (FT.)	PRESSURE (MM. HG)					ALTITUDE (FT.)	PRESSURE (MM. HG)
0	760	Normal (6 lobes) 100%	1	30,500	10	30,400	221.6
1,000	733		2	30,500	10		
5,000	632.4		3	29,500	10		
10,000	522.6		4	32,000	8		
15,000	428.8		4	29,500	11		
20,000	349.2	3 lobes 38%	917	32,000	6	30,000	225.6
25,000	282		993	32,000	7		
30,000	225.6		3	25,000	7		
35,000	178.7		637	31,000	9		
40,000	140.7		871	30,000	9		
		2 lobes 23%	636	27,500	4	26,000	269.8
			869	24,500	6		
		1 lobe 15%	635	26,500†	5	25,833	272
			621	25,000‡	6		
			695	26,000	10		

*From Rasmussen, R. A., Adams, W. E., and Hrdina, L. S.: SURGERY **10**: 85, 1941.
†Failed to recover.
‡Did not become unconscious.

The above findings are in agreement with data more recently accumulated in our laboratory.[86, 92] A more severe strain was placed on the cardiorespiratory function by reducing the lung function to as little as one upper lobe or approximately 15 per cent of normal. Studies of the blood revealed findings similar to those of Andrus and Heuer. A second series of dogs was subjected to extremely rarefied atmospheres by placing them in a chamber in which the pressure could be reduced. Normal dogs when subjected to this procedure were able to

tolerate a reduction in pressure to approximately 221.6 mm. Hg (altitude of 30,400 feet) or a pressure similar to that tolerated by man[97] before becoming unconscious. The same results were obtained when dogs with three lung lobes functioning (both upper lobes and the right middle, or about 38 per cent of normal) were subjected to the test. When one-lobe dogs were subjected to the procedure they became unconscious at 272 mm. Hg pressure (altitude 25,833 feet), thus showing a high reserve in spite of the fact that little lung tissue was functioning. Dogs with one lung lobe functioning have been observed for more than three years and appear to be better compensated at the end of that time than immediately or a few weeks after surgery.

RESULTS OF SURGICAL TREATMENT DURING THE PAST DECADE

An appraisal of the accomplishments of any surgical procedure by the use of statistical material is usually far from satisfactory. However, some information can be gained from reports of personal experiences or collected cases which have appeared in the literature. Thus a monograph by Crafoord in 1938 presented a detailed report on 12 pneumonectomies for carcinoma of the lung with 3 successful results. He discussed the cause of failure in the remaining patients and described the technique developed during this experience. In 1939 Ochsner and DeBakey[47] discussed the results in 7 personal and 76 collected cases by twenty-three authors reported since 1933. Of these, 32 had survived more than 2 months and 25 were living at the time of the report. In 1940 Overholt and Rumel[98] reported the results of a personal series of 17 pneumonectomies with 11 recoveries. Of these 8 were living and without evidence of recurrence or metastases up to as long as 6¼ years following operation.

In 1941 at the twenty-fourth annual meeting of the American Association for Thoracic Surgery this subject was thoroughly discussed and the following statistics were given: E. F. Bulter, 16 pneumectomies with 11 recoveries; E. A. Graham, 35 successful pneumonectomies with patients living without evidence of tumor at the present time: 1 for 8+ years, 1 for 6+ years, 2 for 5+ years, 11 for 3+ years, and 20 for more than 1½ years; his mortality for the past 18 months (20 cases) was 25 per cent; prior to this it had at one time been as low as 12.5 per cent; S. W. Harrington, 9 pneumonectomies with 6 recoveries; R. H. Overholt, 28 pneumonectomies with 20 recoveries during the past 8 years; the mortality rate which was 44 per cent during the first 3 years dropped to 21 per cent during the last 5 years; W. E. Rienhoff, Jr., 52 pneumonectomies with a mortality of 25 per cent during the past 8 years; N. S. Shenstone reported the results in 13 pneumonectomies; prior to January, 1938, there were 4 operations with 2 recoveries; since that date there have been 9 operations with 7 recoveries; at the University of Chicago Clinics there have been 6 pneumonectomies with 3 recoveries, the longest living and well over 4½ years.

These statistics represent only a fraction of the total number of successful cases obtained both in America and abroad and are intended only to emphasize what has been accomplished by a small group of surgeons. The mortality rate per se is not prohibitive and to a great extent depends on the choice of patients for surgery, and the surgeon's specialized training in the management of diseases of the thorax. Of great importance is the gradually increasing number of survivals of more than five years, the longest being over eight years.

It is thus very obvious that real progress has been made in the surgical management of carcinoma of the lung. However, it is only the beginning, and one of the main hazards to its continued advancement, as pointed out by Graham, is the development of a pessimistic attitude among those qualified for and actively engaged in the treatment of these patients. Statistical results in pioneer work on a previously hopeless problem are bound to be discouraging. However, when one considers that all accomplishments have been made within one decade, it compares very favorably with the treatment of malignant disease elsewhere in the body. Undoubtedly continued improvement can and will be achieved. Earlier diagnoses and correlation of the pathologic picture with its clinical significance will be a big step in this direction.

REFERENCES

1. Churchill, E. D.: The Surgical Treatment of Carcinoma of the Lung, J. Thoracic Surg. **2**: 254, 1933.
2. Carlson, Herbert A., and Ballon, Harry C.: The Operability of Carcinoma of the Lung, J. Thoracic Surg. 2: 323, 1933.
3. Sauerbruch, F.: Chirurgie der Brustorgane, Berlin, 1920, Julius Springer, vol. I., p. 849.
4. Gluck, T.: Experimenteller Beitrag. zur Frage der Lungen Extirpation, Berl. klin. Wchnschr. **18**: 645, 1881.
5. Réclus, M.: Address at the French Surgical Congress, 1895.
6. Paget, Stephen: The Surgery of the Chest, Bristol, 1896, John Wright and Co., pp. 207, 398-407.
7. Vesalius, Andreas: Cited by Homans, John: A Textbook of Surgery, Springfield, 1931, Charles C Thomas, Publisher, p. 760.
8. Killian, Prof. Hans: Scope and Utility of Differential Pressure in Thoracic Surgery, Anesth. & Analg. **17**: 154, 1938.
9. Sauerbruch, F.: Present Status of Surgery of the Thorax, J. A. M. A. **51**: 808, 1908.
10. Meltzer, S. J., and Auer, J.: Continuous Respiration Without Respiratory Movements, J. Exper. Med. **11**: 622, 1909.
11. Elsberg, Charles A.: Clinical Experiences With Intratracheal Insufflation (Meltzer) With Remarks Upon the Method for Thoracic Surgery, Ann. Surg. **52**: 23, 1910.
12. Elsberg, Charles A.: Further Experiences With Anesthesia by the Intratracheal Insufflation of Air and Ether, Ann. Surg. **53**: 749, 1911.
13. Graham, E. A., and Bell, R. D.: Open Pneumothorax, Am. J. M. Sc. **156**: 839, 1918.
14. Sauerbruch, F.: Zentralbl. f. Clin., Leipzig, 1904.
15. Duval: Gunshot Wounds of the Lung, Paris, 1917, Masson et Cie., Presse méd., 1922.
16. Edwards, A. Tudor: Tumours of the Lung, Brit. J. Surg. **26**: 166, 1938.
17. Adams, W. E.: Subtotal Atelectasis and Pneumonectomy in Dogs, Proc. Soc. Exper. Biol. & Med. **28**: 957, 1931.
18. Fraenckner, P., and Bjorkman, S.: Proc. Roy. Soc. Med. **30**: 477, 1937.
19. Rolandus: Quoted by Murphy, J. B.: Surgery of the Lung, J. A. M. A. **31**: 341, 1898.

20. Gluck, T.: Experimenteller Beitrag. zur Frage der Lungen Extirpation, Berl. klin. Wchnschr. **18**: 645, 1881.
21. Friedrich, P. L.: Ueber den Raumausgleich in der Brusthohle nach einseitiger Lungenamputation, nebst. Bemerkungun über das operative Mediastinal-emphysem, Verhandl. d. deutsch. Gesselsch. f. Chir. **37**: 571, 1908.
22. Adams, W. E., and Livingstone, H. M.: Lobectomy and Pneumectomy in Dogs, Experimental Surgery, Arch. Surg. **25**: 898, 1932.
23. Graham, E. A., and Singer, J. J.: Successful Removal of an Entire Lung for Carcinoma of Bronchus, J. A. M. A. **101**: 1371, 1933.
24. Bettman, R. B.: A Study of the Factors Concerned in Failure of the Bronchi to Heal, Arch. Surg. **8**: 418, 1924.
25. Adams, W. E., and Livingstone, H. M.: Bronchial Injury and Repair. An Experimental Study, Ann. Surg. **91**: 342, 1930.
26. Drastich, L., Adams, W. E., Hastings, A. B., and Compere, C. L.: The Effect of Exercise on the Acid-Base Balance and Oxygen of the Blood Following Atelectasis and Pneumectomy, J. Thoracic Surg. **3**: 341, 1934.
27. Carter, B. N., Longacre, J. J., and Quill, L. McG.: A Study of the Changes in Cardiorespiratory Physiology Following Total Pneumonectomy in Young Developing Animals, J. Thoracic Surg. **7**: 329, 1938.
28. Heuer, George J., and Dunn, George R.: Experimental Pneumonectomy, Bull. Johns Hopkins Hosp. **31**: 31, 1920.
29. Roentgen, W. C.: Concerning a New Kind of Ray (Physikalische Institute der Universitat, Wurtzburg, 1895), Am. J. Roentgenol. **10**: 320, 1923.
30. Clerf, Louis, H.: Foreign Bodies in the Air Passages, Ann. Med. Hist. **8**: 547, 1936.
31. Arkin, Aaron, and Wagner, David H.: Primary Carcinoma of the Lung. A Diagnostic Study of One Hundred and Thirty-Five Cases of Four Years, J. A. M. A. **106**: 587, 1936.
32. Seyforth, C.: Lungenkarzionon in Leipzig, Deutsche med. Wchnschr. **50**: 1497, 1924.
33. Sharp, G.: The Diagnosis of Primary Carcinoma of the Lung by Aspiration, Am. J. Cancer **15**: 853, 1931.
34. Koletsky, S.: Primary Carcinoma of the Lung. A Clinical and Pathologic Study of 100 Cases, Arch. Int. Med. **62**: 636, 1938.
35. Simons, E. J.: Primary Carcinoma of the Lung, Chicago, 1937, The Year Book Publishers, Inc.
36. Overholt, R. H.: Curability of Primary Carcinoma of the Lung, Surg., Gynec. & Obst. **70**: 479, 1940.
37. Tuttle, W. McC., and Womack, N. A.: Bronchogenic Carcinoma: A Classification in Relation to Treatment and Prognosis, J. Thoracic Surg. **4**: 125, 1934.
38. Halpert, B.: Pathology of Bronchogenic Carcinoma, New Orleans M. & S. J. **91**: 439, 1939.
39. Rabinovitch, Jacob, Hochberg, Lew A., and Lederer, Max: Primary (Bronchiogenic) Carcinoma of the Lung. With a Histopathologic Study of Forty Necropsies, J. Thoracic Surg. **9**: 332, 1940.
40. Gebauer, Paul W.: The Differentiation of Bronchiogenic Carcinomas, J. Thoracic Surg. **10**: 373, 1941.
41. Hauser, Harry, and Wolpaw, Sidney, E.: Cavitary Bronchogenic Carcinoma, Radiology **34**: 698, 1940.
42. Adams, W. E., Steiner, Paul E., and Bloch, Robert G.: Carcinoma of the Lung With Long Clinical Course, SURGERY. In press.
43. Churchill, E. D.: Thoracic Surgery, New England J. Med. **220**: 998, 1939.
44. Edwards, A. Tudor, and Taylor, A. Brian: Vascular Endothelioma of the Lung, Brit. J. Surg. **25**: 487, 1938.
45. Tuffier, T.: Bull. et mém. soc. de chir., Paris **34**: 879, 1908.
46. Sauerbruch, F.: Personal communication.
47. Ochsner, Alton, and DeBakey, Michael: Primary Pulmonary Malignancy. Treatment by Total Pneumonectomy; Analysis of 79 Collected Cases and Presentation of 7 Personal Cases, Surg., Gynec. & Obst. **68**: 435, 1939.
48. Graham, Evarts A.: Remarks on Carcinoma of the Lung, South. M. J. **21**: 199, 1928.
49. Dudgeon, L. S.: J. Laryngol. & Otol. **50**: 752, 1935.
50. Goldman, Alfred: II. Cytology of Serous Effusions, With Special Reference to Tumor Cells, Arch. Surg. **19**: 1672, 1929.
51. Singer, J. J.: Thoracic Tumors; A Roentgen Study, Arch. Surg. **18**: 283, 1929.
52. Mason, George A.: The Clinical and Surgical Aspects of Thoracic Neoplasms, Proc. Roy. Soc. Med. **32**: 1346, 1939.

53. Bloch, R. G., and Bogardus, G.: Bronchogenic Carcinoma, With Special Reference to Results With Roentgen Therapy, Arch. Int. Med. **66**: 39, 1940.
54. Steiner, Paul E.: Effects of Roentgen Therapy on Histologic Picture and on Survival in Cases of Primary Carcinoma of Lung, Arch. Int. Med. **66**: 140, 1940.
55. Adler, I.: Primary Malignant Growths of the Lungs and Bronchi, London, 1912, Longmans, Green and Co.
56. Stephens, H. Brodie: A Consideration of Contralateral Pneumothorax as a Complication of Intrathoracic Operations, J. Thoracic Surg. **5**: 471, 1936.
57. Bradshaw, H. H.: Anesthesia for Intrathoracic Operations, J. Thoracic Surg. **8**: 293, 1939.
58. Bourne, Wesley: Personal communication.
59. Heidrick, Fausteena, Adams, W. E., and Livingstone, H. L.: Spontaneous Pneumothorax Following Positive Pressure Intratracheal Anesthesia: Report of a Case, Arch. Surg. **41**: 65, 1940.
60. Macklin, C. C.: Pneumothorax With Massive Collapse From Experimental Local Over-Inflation of the Lung Substance, Canad. M. A. J. **36**: 414, 1937.
61. Macklin, C. C.: Transport of Air Along Sheaths of Pulmonic Blood Vessels From Alveoli to Mediastinum, Arch. Int. Med. **64**: 913, 1939.
62. Marcotte, R. J., Phillips, F. J., Adams, W. E., and Livingstone, H.: Differential Intrabronchial Pressures and Mediastinal Emphysema, J. Thoracic Surg. **9**: 346, 1940.
63. O'Shaughnessy, Laurence: The Vagus and Its Relation to the Surgery of the Lung, J. Thoracic Surg. **5**: 386, 1936.
64. Rienhoff, W. F., Jr.: The Treatment of Carcinoma of the Lung, S. Clin. North America **16**: 1459, 1936.
65. Ohsawa, T.: The Surgery of the Esophagus, From the Surgical Clinics of Prof. R. Torikota and Prof. Isobe, Kyote Imperial University, 1934.
66. Phillips, Francis, Livingstone, H. M., and Adams, W. E.: A Clinical Consideration of Anesthesia in Intrathoracic Operations, Anesth. & Analg. **20**: 78, 1941.
67. Rienhoff, William F., Jr.: Technique of Total Pneumonectomy and Lobectomy. Presented at the Inter-State Post-Graduate Medical Assembly of North America, November 5-9, 1934, Philadelphia, Pa.
68. Adams, W. E.: Pneumonectomy for Bronchogenic Carcinoma of the Lung. Report of a Successful Case 16 Months After Operation, Illinois M. J., **74**: 442, 1938.
69. Rienhoff, William F., Jr.: Graded Pneumonectomy in the Treatment of Tumors of the Lung, Bull. Johns Hopkins Hosp. **64**: 167, 1939.
70. Edwards, F. Ronald: Studies in Pneumonectomy and the Development of a Two-Stage Operation for the Removal of a Whole Lung, Brit. J. Surg. **27**: 392, 1939.
71. Graham, E. A.: Discussion of paper by Rienhoff, William F., Jr.: Intrathoracic Anatomical Readjustments Following Complete Ablation of One Lung, J. Thoracic Surg. **6**: 254, 1937.
72. Overholt, Richard H.: Surgical Treatment of Carcinoma of the Lung, Surg., Gynec. & Obst. **64**: 209, 1937.
73. Rienhoff, William F., Jr.: The Surgical Technic of Total Pneumonectomy, Arch. Surg. **32**: 218, 1936.
74. Crafoord, Clarence: On the Technique of Pneumonectomy in Man. A Critical Survey of the Experimental and Clinical Development and a Report of the Author's Material and Technique. From Surgical Clinic II of the Sabbatsberg Hospital, Stockholm, 1938.
75. Dorsey, John: Personal communication.
76. Monod, R.: Rap. de l'assoc. française de chir., Paris, 1936.
77. Morrison, J. T.: Brit. J. Surg. **14**: 94, 1926.
78. Nissin, Zentralbl. f. Chir. **47**: 1003, 1931.
79. O'Shaughnessy, L.: Lancet **1**: 185, 1935.
80. Rienhoff, William F., Jr.: A New Operative Technique for Closure of the Main Bronchus, Bull. Johns Hopkins Hosp. **60**: 372, 1937.
81. Harrington, S. W.: Pneumonectomy for Carcinoma of the Lung, presented at the 24th Annual Meeting of the American Association for Thoracic Surgery at Toronto, June, 1941.
82. Hambrecht, F. E.: Personal communication.
83. Rienhoff, William F., Jr.: Readjustments in the Thoracic Cage and Its Contents Following Total and Partial Pneumonectomy, South. M. J. **29**: 445, 1936.

84. Rienhoff, William F., Jr.: Intrathoracic Anatomical Readjustments Following Complete Ablation of One Lung, J. Thoracic Surg. **6**: 254, 1937.
85. Phillips, F. J., and Adams, W. E.: Obliteration of the Pleural Space Following Pneumonectomy, Ann. Surg. **113**: 221, 1941.
86. Phillips, F. J., Adams, W. E., and Hrdina, L. S.: Physiologic Adjustment in Sublethal Reduction of Lung Capacity in Dogs, SURGERY **9**: 25, 1941.
87. Graham, E. A.: Personal communication.
88. Rienhoff, W. F., Reichert, F. L., and Heuer, G. J.: Compensatory Changes in the Remaining Lung Following Total Pneumonectomy, Bull. Johns Hopkins Hosp. **57**: 373, 1935.
89. Hibber: Morphol. Jahrb. **74**: 171, 1934.
90. Longacre, J. J., and Johansmann, Ralph: An Experimental Study of the Fate of the Remaining Lung Following Total Pneumonectomy, J. Thoracic Surg. **10**: 131, 1940.
91. Behrend, A., and Mann, F. C.: J. Thoracic Surg. **6**: 684, 1937.
92. Rasmussen, Richard A., Adams, W. E., and Hrdina, Leo: Should the Pleural Space Be Reduced in Size in the Resection of Lung Tissue? SURGERY **10**: 85, 1941.
93. Heuer, G. J., and Andrus, W. D. W.: The Alveolar and Blood Gas Changes Following Pneumonectomy, Bull. Johns Hopkins Hosp. **33**: 130, 1922.
94. Andrus, W. D. W.: Observations on the Total Lung Volume and Blood Flow Following Pneumonectomy, Bull. Johns Hopkins Hosp. **34**: 119, 1923.
95. Andrus, W. D. W.: Observations of the Cardiorespiratory Physiology Following the Collapse of One Lung by Bronchial Ligation, Arch. Surg. **10**: 506, 1925.
96. Longacre, J. J., Carter, H. N., and Quill, L. M.: An Experimental Study of Some of the Physiologic Changes Following Total Pneumonectomy, J. Thoracic Surg. **6**: 237, 1937.
97. Armstrong, Harry G.: Principles and Practice of Aviation Medicine, Baltimore, 1939, Williams and Wilkins Co.
98. Overholt, Richard H., and Rumel, William Ray: Clinical Studies of Primary Carcinoma of the Lung. An Analysis of Seventy-Five Cases, Twenty-One of Which Were Treated by Pneumonectomy or Lobectomy, J. A. M. A. **114**: 735, 1940.

Book Reviews

Infantile Paralysis: Anterior Poliomyelitis. By Philip Lewin, M.D., Associate Professor of Bone and Joint Surgery, Northwestern University Medical School; Professor Orthopedic Surgery, Cook County Graduate School of Medicine; Attending Orthopedic Surgeon, Cook County and Michael Reese Hospitals; Consulting Orthopedic Surgeon, Municipal Contagious Disease Hospital, Chicago. Cloth. Pp. 372, with 165 illustrations. Philadelphia, 1941, W. B. Saunders Co. $6.

The author has produced a volume on the subject of poliomyelitis which should be widely used as a handbook and guide both for physicians who may be especially interested in the diagnosis and treatment of the disease and for the general practitioner whose interest may be only casual and occasional. It covers the subject from the standpoint of etiology, resistance and immunity, epidemiology, pathology, symptomatology and treatment, both during the immediate convalescent stage and the stages of late convalescence and operative treatment.

The author has borrowed freely from the writings of others and in fact has included in the material sections by numerous authors of prominence whose experience gives authority to their portion of the text.

The arrangement of this book seems excellent to the reviewer. It is adequately and well illustrated. It is not too large and the chapters are not too long so that it should be a useful textbook and handbook for those interested in this disease.

Infantile Paralysis: A Symposium Delivered at Vanderbilt University, April, 1941. Cloth. Pp. 293, with 47 illustrations. New York, 1941, The National Foundation for Infantile Paralysis, Inc.

Recent advances in our knowledge of infantile paralysis are due in large measure to the liberal aid which the National Foundation for Infantile Paralysis has given to various groups of workers. The present volume, representing another activity sponsored by the Foundation, constitutes six lectures delivered at Vanderbilt University by outstanding authorities in the field. Each of the lectures makes up a chapter. Chapter I is on the "History of Poliomyelitis Up to the Present Time," by Professor P. F. Clark of the University of Wisconsin Medical School. Chapter II is by Dr. Charles Armstrong, Senior Surgeon, United States Public Health Service, on "The Etiology of Poliomyelitis." Chapter III on the "Immunological and Serological Phenomena in Poliomyelitis" is by Dr. T. M. Rivers, Director, the Hospital of the Rockefeller Institute for Medical Research. "The Pathology and Pathogenesis of Poliomyelitis" forms Chapter IV, and is written by Dr. E. W. Goodpasture of Vanderbilt University School of Medicine. Chapter V is a discussion of "The Epidemiology of Poliomyelitis," by Dr. J. R. Paul of Yale University School of Medicine. The final chapter is by Dr. F. R. Ober of Harvard University on "Treatment and Rehabilitation of the Poliomyelitis Patient."

Each of the chapters is well documented. The bibliography is placed at the end of the last lecture and numbers 575 references. The subject is presented in a

lucid and scholarly manner. There is considerable overlapping of material in some of the lectures which could have been obviated by more careful editing. This repetition may have served the lecturers well, but it dulls the readers' interest. The volume is well indexed.

The contents of the volume are authoritative and the monograph is highly recommended to anyone desiring a comprehensive statement concerning the present-day problem of infantile paralysis. The National Foundation for Infantile Paralysis, Inc., is to be commended for undertaking such a project.

Erratum

On page 687 of the October, 1941, issue in the "Report of the Meeting of the American Association for Thoracic Surgery, June 9-11, 1941, Toronto, Ontario" by John R. Paine, M.D., Minneapolis, Minn., reference is made to the Ross-Lambert Prize Essay read by C. A. Moyer, Boston. The award should appear as the Rose Lampert Graff Foundation Prize Essay.